

***BIFUNCTIONAL HETEROCYCLIC COMPOUNDS AND
METHODS OF MAKING AND USING SAME***

RELATED APPLICATIONS

This application incorporates by reference and claims priority to U.S. Patent Application Nos. 60/414,207, filed September 26, 2002, and 60/448,216, filed February 19, 2003.

FIELD OF THE INVENTION

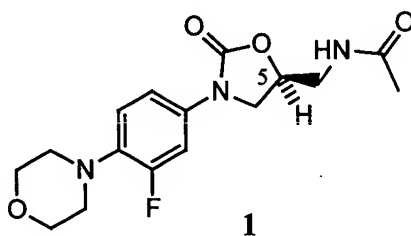
The present invention relates generally to the field of anti-infective, anti-proliferative, anti-inflammatory, and prokinetic agents, and more particularly, the invention relates to a family of bifunctional heterocyclic compounds useful as such an agent.

BACKGROUND

The evolution of strains of cells or organisms resistant to currently effective therapeutic agents is an ongoing medical problem. For example, the development of cancerous cells resistant to chemotherapeutic drugs has long been recognized as a problem in the oncology field. Once resistant cells develop, the therapeutic regime, in order to remain effective, must be modified to introduce other chemotherapeutic agents. Another example of this resistance problem is the development of strains of microbial, fungal, parasitic and viral pathogens resistant to one or more anti-infective agents. As a result, there is still a need for new anti-proliferative and anti-infective agents that are effective against strains of cells or organisms that have developed resistance to currently available agents.

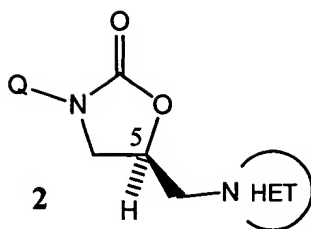
In the field of anti-infective agents, a variety of different antibiotics have been developed and approved for use in humans over the years. An oxazolidinone ring containing antibiotic known as linezolid (see, compound 1), available under the trade name Zyvox[®], has been approved for use as an anti-bacterial agent active against Gram-positive organisms.

Unfortunately, linezolid resistant strains of organisms are already being reported (Tsiodras *et al.* (2001) LANCET 358: 207; Gonzales *et al.* (2001) LANCET 357: 1179; Zurenko *et al.* (1999) PROCEEDINGS OF THE 39TH ANNUAL INTERSCIENCE CONFERENCE ON ANTIBACTERIAL AGENTS AND CHEMOTHERAPY (ICAAC); San Francisco, CA, USA, September 26-29).

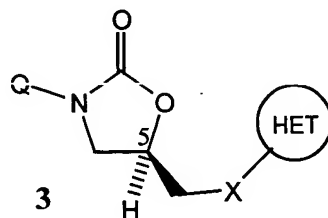


Because linezolid is both a clinically effective and commercially significant anti-microbial agent, investigators have been working to develop other effective linezolid derivatives. Research has indicated that the oxazolidinone ring is important for linezolid activity. The literature commonly describes molecules having small groups substituted at the C-5 of the oxazolidinone ring, and early structure-activity relationships suggested that compounds with larger groups at the C-5 position were less active as anti-bacterial agents. As a consequence, it is believed that, in general, investigators have been reluctant to place large substituents at the C-5 position of oxazolidinone rings in anti-microbial agents.

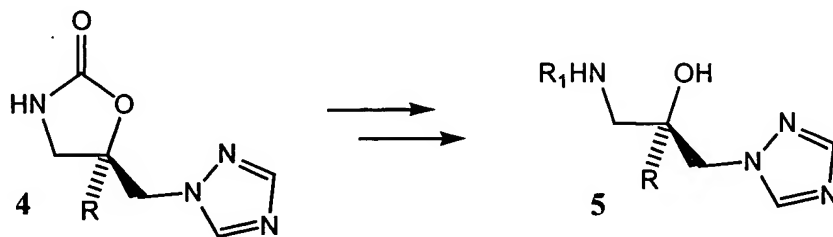
International patent publication no. WO 01/81350 discloses a series of C-5 substituted oxazolidinones (see, general structure 2) where the acetamido group of linezolid was replaced, for example, with an optionally substituted N-linked 5-membered heteroaryl ring or an N-linked 6-membered heteroaryl ring. The 5-membered heteroaryl ring may contain either (i) one to three further nitrogen heteroatoms, or (ii) a further heteroatom selected from O and S together with an optional further nitrogen heteroatom; wherein the ring is optionally substituted on a C-atom by an oxo or thioxo group; and/or is optionally substituted on a C-atom by one or two C₁₋₄ alkyl groups; and/or on an available nitrogen atom (provided that the ring is not thereby quaternized) by C₁₋₄ groups. The N-linked 6-membered heteroaryl ring may contain up to three nitrogen heteroatoms in total, wherein the ring is substituted on a suitable C-atom by oxo or thioxo groups, and optionally substituted on any available C-atom by one or two C₁₋₄ alkyl groups.



In addition, International patent publication nos. WO 99/64416 and WO 00/21960 also disclose a series of 5-substituted oxazolidinones (see, general structure 3). In particular, WO 99/64416 discloses compounds having the general structure 3, where X is -O- or -S- and HET is a C-linked 6-membered heteroaryl ring containing 1 or 2 nitrogen atoms. WO 00/21960 discloses compounds having the general structure 3, where X is -N(H)- and HET is a C-linked 5-membered heteroaryl ring containing 2 to 4 heteroatoms independently selected from N, O and S.

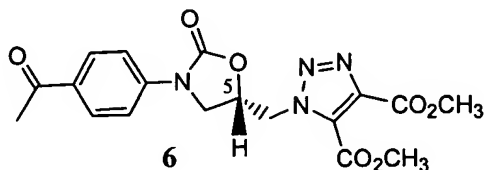


European Patent no. 0 097 469 B1 discloses intermediates of compound 4 which are useful in the synthesis of triazole anti-fungal agents of general structure 5. The intermediates may contain a disubstituted C-5 atom in the oxazolidinone ring, and the nitrogen atom of the oxazolidinone ring is a secondary amine.

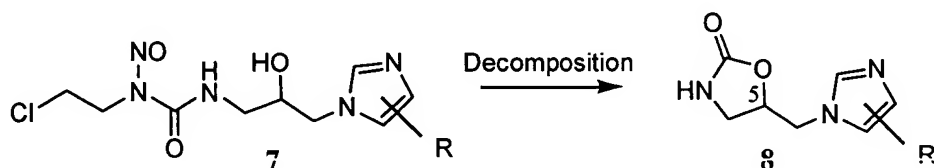


Gregory and coworkers disclose the synthesis of a variety of oxazolidinone containing antibacterial agents (Gregory *et al.* (1989) J. MED. CHEM. 32: 1673-1681). Compound 6, a C-5 substituted five-membered heteroaryl derivative, was inactive as an antibacterial agent. This

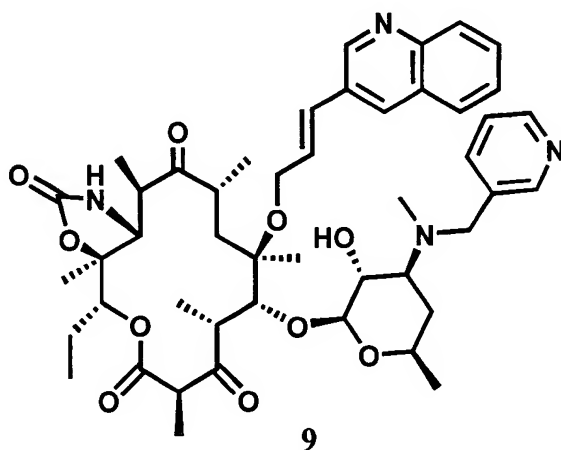
observation appears to be consistent with other oxazolidinone containing compounds that have the opposite stereochemical configuration at C-5 relative to that found in linezolid.



Oxazolidinone compounds similar to those of compound 8 have been formed via decomposition of substituted nitrosoureas 7 and have been useful as anticancer agents (Mulcahy *et al.* (1989) EUR J. CLIN. ONCOL. 5: 1099-1104; Carmiati *et al.* (1989) BIOCHEM. PHARMACOL. 38: 2253-2258).

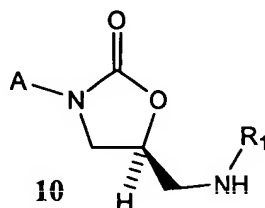


US Patent 6,034,069 discloses a series of 3'-N-modified 6-O-substituted erythromycin ketolide derivatives similar to compound 9. The aryl group attached to the aminosaccharide moiety (represented by a 3-pyridyl group in 9) was variable, and non-aryl substituents were synthesized as well.



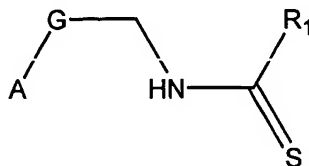
Published German patent application DE 196 04 223 A1 discloses oxazolidinone ring-containing compounds of the general structure **10**, where R₁ can be, in addition to other structures, a substituted or unsubstituted five-membered ring chosen from thienyl, furyl, pyrrolyl, pyrazolyl, thiazolyl, oxazolyl, imidazolyl and pyrrolidinyl.

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U.S. Patent No. 6,362,189 discloses antibiotic compounds having the general formula **11**. To the extent that the chemical moiety denoted by the symbol "G" may be an oxazolidinone ring, the ring may be substituted with a thiocarbonyl functionality, namely a -CH₂NHC(S)R₁.

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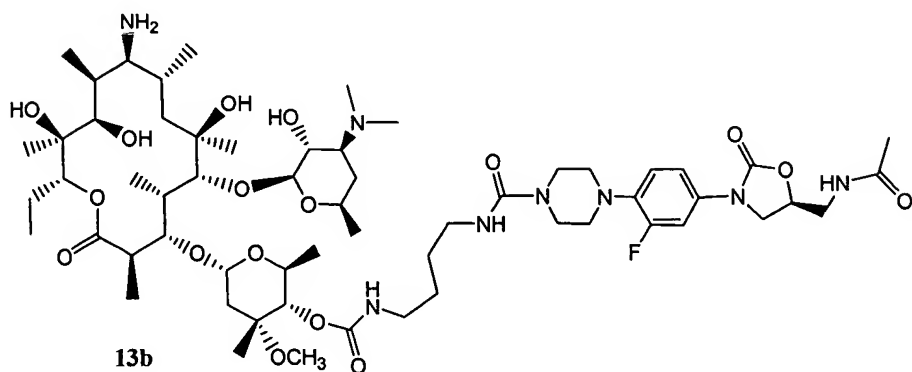
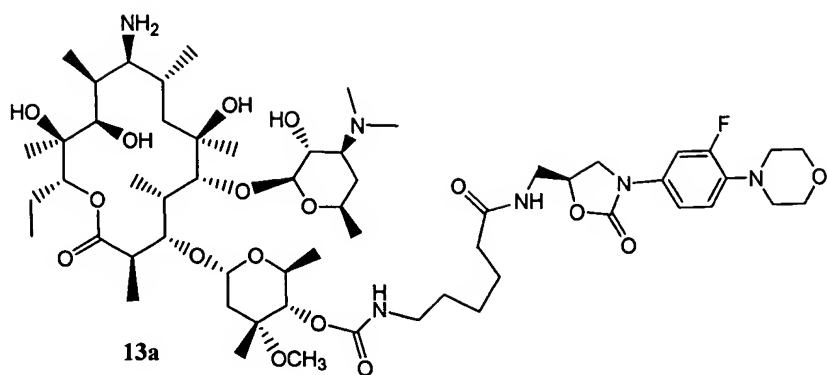


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International patent publication no. WO 99/63937 proposes the synthesis of multivalent macrolide antibiotics comprising a portion of a macrolide antibiotic linked via a linker to a portion of another known antibacterial agent. Two of the compounds proposed, although

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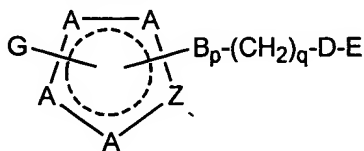
apparently not made or tested, include those shown below having the formulas **13a** and **13b**.



Notwithstanding the foregoing, there is still an ongoing need for new anti-infective and anti-proliferative agents. There is also an ongoing need for new anti-inflammatory agents, and
 5 new agents to treat gastrointestinal motility disorders.

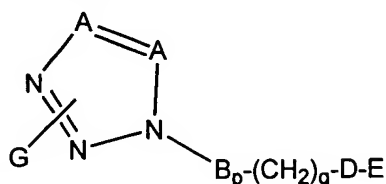
SUMMARY OF THE INVENTION

The invention provides a family of compounds useful as anti-infective agents and/or anti-proliferative agents, for example, chemotherapeutic agents, anti-fungal agents, anti-bacterial
 10 agents, anti-parasitic agents, anti-viral agents, and/or anti-inflammatory agents, and/or prokinetic (gastrointestinal modulatory) agents, having the formula:



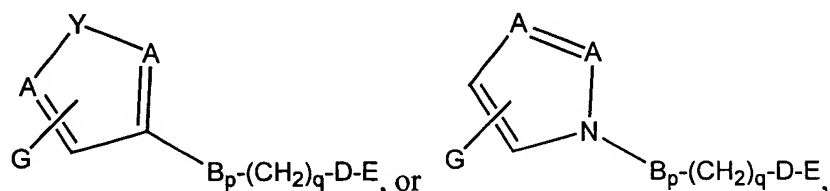
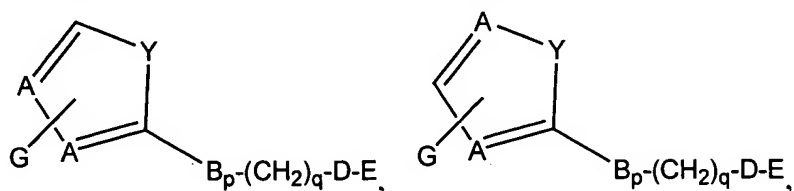
or pharmaceutically acceptable salts, esters, or prodrugs thereof. In the formula, p and q
 15 independently are 0 or 1. Also, A, at each occurrence, independently is a carbon atom, a carbonyl group, or a nitrogen atom. The B, D, E, and G groups can be selected from the respective groups of chemical moieties later defined in the detailed description.

In some embodiments, the invention provides a family of compounds having the formula:



or pharmaceutically acceptable salts, esters or prodrugs thereof. In the formula, p and q independently are 0 or 1. Also, A, at each occurrence, independently is a carbon atom or a nitrogen atom, provided that when one A is a nitrogen atom, the other A is a carbon atom. The B, D, E, and G groups can be selected from the respective groups of chemical moieties later defined in the detailed description.

In other embodiments, the invention provides a family of compounds having the formula:



or pharmaceutically acceptable salts, esters or prodrugs thereof. In the formula, p and q independently are 0 or 1. Also, A, at each occurrence, independently is a carbon atom or a nitrogen atom. The B, D, E, and G groups can be selected from the respective groups of chemical moieties later defined in the detailed description.

In another aspect, the invention provides a pharmaceutical composition comprising a therapeutically effective amount of one or more of the foregoing compounds and a pharmaceutically acceptable carrier. In yet another aspect, the invention provides a method for treating a microbial infection, a fungal infection, a viral infection, a parasitic disease, a proliferative disease, an inflammatory disease, or a gastrointestinal motility disorder in a mammal by administering effective amounts of the compounds of the invention or pharmaceutical compositions of the invention, for example, via oral, parenteral, or topical routes. In still another aspect, the invention provides methods for synthesizing any one of the foregoing

compounds. In another aspect, the invention provides a medical device, for example, a medical stent, which contains or is coated with one or more of the foregoing compounds.

The foregoing and other aspects and embodiments of the invention may be more fully understood by reference to the following detailed description and claims.

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DETAILED DESCRIPTION OF THE INVENTION

The present invention provides a family of compounds that can be used as anti-proliferative agents and/or anti-infective agents. The compounds may be used without
10 limitation, for example, as anti-cancer agents, anti-bacterial agents, anti-fungal agents, anti-parasitic agents and/or anti-viral agents. Further, the present invention provides a family of compounds that can be used without limitation as anti-inflammatory agents, for example, for use in treating chronic inflammatory airway diseases, and/or as prokinetic agents, for example, for use in treating gastrointestinal motility disorders such as gastroesophageal reflux disease,
15 gastroparesis (diabetic and post surgical), irritable bowel syndrome, and constipation.

1. Definitions

For the purpose of the present invention, the following definitions have been used throughout.

20 The carbon content of various hydrocarbon containing moieties is indicated by a prefix designating the minimum and maximum number of carbon atoms in the moiety, i.e., the prefix C_{i-j} defines the number of carbon atoms present from the integer "i" to the integer "j", inclusive. Thus, C₁₋₄ alkyl refers to alkyl of 1-4 carbon atoms, inclusive, or methyl, ethyl, propyl, and butyl, and isomeric forms thereof.

25 The terms "C₁₋₂ alkyl", "C₁₋₃ alkyl", "C₁₋₄ alkyl", "C₁₋₅ alkyl", "C₁₋₆ alkyl", "C₁₋₈ alkyl", "C₁₋₁₀ alkyl", and "C₁₋₁₆ alkyl" refer to an alkyl group having one to two, one to three, one to four, one to five, one to six, one to eight, one to ten, or one to sixteen carbon atoms, respectively such as, for example, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, undecyl, dodecyl, tridecyl, tetradecyl and their isomeric forms thereof.

30 The terms "C₂₋₅ alkenyl", "C₂₋₆ alkenyl", "C₂₋₈ alkenyl", and "C₂₋₁₆ alkenyl" refer to at least one double bond alkenyl group having two to five, two to six, two to eight, or two to sixteen

carbon atoms, respectively such as, for example, ethenyl, propenyl, butenyl, pentenyl, pentdienyl, hexenyl, hexadienyl, heptenyl, heptdienyl, octenyl, octdienyl, octatrienyl, nonenyl, nonedienyl, nonatrienyl, undecenyl, undecdienyl, dodecenyl, tridecenyl, tetradecenyl and their isomeric forms thereof.

5 The terms "C₂₋₅ alkynyl", "C₂₋₆ alkynyl", and "C₂₋₈ alkynyl" refer to at least one triple bond alkynyl group having two to five, two to six, or two to eight carbon atoms, respectively such as, for example, ethynyl, propynyl, butynyl, pentynyl, pentdiynyl, hexynyl, hexdiynyl, heptynyl, heptdiynyl, octynyl, octdiynyl, octatriynyl, and their isomeric forms thereof.

10 The terms "C₃₋₄ cycloalkyl", "C₃₋₆ cycloalkyl", "C₅₋₆ cycloalkyl", "C₃₋₇ cycloalkyl", and "C₃₋₈ cycloalkyl" refer to a cycloalkyl group having three to four, three to six, five to six, three to seven, or three to eight carbon atoms, respectively such as, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, and their isomeric forms thereof.

15 The terms "C₁₋₄ alkoxy", "C₁₋₅ alkoxy", "C₁₋₆ alkoxy", and "C₁₋₈ alkoxy", refer to an alkyl group having one to four, one to five, one to six, or one to eight carbon atoms, respectively attached to an oxygen atom such as, for example, methoxy, ethoxy, propyloxy, butyloxy, pentyloxy, hexyloxy, heptyloxy, or octyloxy and their isomeric forms thereof.

 The term "C₁₋₆ hydroxy" refers to an alkyl group having one to six carbon atoms, and isomeric forms thereof, attached to a hydroxy group.

20 The terms "C₁₋₃ acyl", "C₁₋₄ acyl", "C₁₋₅ acyl", "C₁₋₆ acyl", and "C₁₋₈ acyl" refer to a carbonyl group having an alkyl group of one to three, one to four, one to five, one to six, or one to eight carbon atoms, respectively.

 The terms "C₁₋₄ alkoxy carbonyl", and "C₁₋₆ alkoxy carbonyl" refer to an ester group having an alkyl group of one to four, or one to six carbon atoms, respectively.

25 The terms "C₁₋₆ alkylthio" and "C₁₋₈ alkylthio" refer to an alkyl group having one to six or one to eight carbon atoms respectively and isomeric forms thereof attached to a sulfur atom.

 The term "C₁₋₃ alkylamino" refers to alkyl groups having from one to three carbon atoms attached to an amino moiety such as, for example, dimethylamino, methylethylamino, diethylamino, dipropylamino, methylpropylamino, or ethylpropylamino and their isomeric forms thereof.

30 The term "Het" refers to 5 to 10 membered saturated, unsaturated or aromatic heterocyclic rings containing one or more oxygen, nitrogen, and sulfur forming such groups as,

for example, pyridine, thiophene, furan, pyrazoline, pyrimidine, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 3-pyridazinyl, 4-pyridazinyl, 3-pyrazinyl, 2-quinolyl, 3-quinolyl, 1-isoquinolyl, 3-isoquinolyl, 4-isoquinolyl, 2-quinazolinyl, 4-quinazolinyl, 2-quinoxalyl, 1-phthalazinyl, 4-oxo-2-imidazolyl, 2-imidazolyl, 4-imidazolyl, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, 3-pyrazolyl, 4-pyrazolyl, 5-pyrazolyl, 2-oxazolyl, 4-oxazolyl, 4-oxo-2-oxazolyl, 5-oxazolyl, 4,5-dihydrooxazole, 1,2,3-oxathiole, 1,2,3-oxadiazole, 1,2,4-oxadiazole, 1,2,5-oxadiazole, 1,3,4-oxadiazole, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 3-isothiazole, 4-isothiazole, 5-isothiazole, 2-indolyl, 3-indolyl, 3-indazolyl, 2-benzoxazolyl, 2-benzothiazolyl, 2-benzimidazolyl, 2-benzofuranyl, 3-benzofuranyl, benzoisothiazole, benzisoxazole, 2-furanyl, 3-furanyl, 2-thienyl, 3-thienyl, 2-pyrrolyl, 3-pyrrolyl, 3-isopyrrolyl, 4-isopyrrolyl, 5-isopyrrolyl, 1,2,3-oxathiazole-1-oxide, 1,2,4-oxadiazol-3-yl, 1,2,4-oxadiazol-5-yl, 5-oxo-1,2,4-oxadiazol-3-yl, 1,2,4-thiadiazol-3-yl, 1,2,4-thiadiazol-5-yl, 3-oxo-1,2,4-thiadiazol-5-yl, 1,3,4-thiadiazol-5-yl, 2-oxo-1,3,4-thiadiazol-5-yl, 1,2,4-triazol-3-yl, 1,2,4-triazol-5-yl, 1,2,3,4-tetrazol-5-yl, 5-oxazolyl, 1-pyrrolyl, 1-pyrazolyl, 1,2,3-triazol-1-yl, 1,2,4-triazol-1-yl, 1-tetrazolyl, 1-indolyl, 1-indazolyl, 2-isoindolyl, 7-oxo-2-isoindolyl, 1-purinyl, 3-isothiazolyl, 4-isothiazolyl and 5-isothiazolyl, 1,3,4-oxadiazole, 4-oxo-2-thiazolinyl, or 5-methyl-1,3,4-thiadiazol-2-yl, thiazolidone, 1,2,3,4-thiatriazole, 1,2,4-dithiazolone. Each of these moieties may be substituted as appropriate.

The terms "halo" or "halogen" refers to a fluorine atom, a chlorine atom, a bromine atom, and/or an iodine atom.

The term "hydroxy protecting group" refers to an easily removable group which is known in the art to protect a hydroxyl group against undesirable reaction during synthetic procedures and to be selectively removable. The use of hydroxy-protecting groups is well known in the art for protecting groups against undesirable reactions during a synthetic procedure and many such protecting groups are known (see, for example, T.H. Greene and P.G.M. Wuts (1999) PROTECTIVE GROUPS IN ORGANIC SYNTHESIS, 3rd edition, John Wiley & Sons, New York). Examples of hydroxy protecting groups include, but are not limited to, acetate, methoxymethyl ether, methylthiomethyl, *tert*-butyldimethylsilyl, *tert*-butyldiphenylsilyl, acyl substituted with an aromatic group and the like.

The term "aryl" refers to a mono- or bicyclic carbocyclic ring system having one or two aromatic rings including, but not limited to, phenyl, naphthyl, tetrahydronaphthyl, indenyl, and the like.

The term "substituted aryl" refers to an aryl group, as defined herein, substituted by independent replacement of one, two, three, four, or five of the hydrogen atoms thereon with substituents independently selected from alkyl, substituted alkyl, haloalkyl, alkoxy, thioalkoxy, amino, alkylamino, dialkylamino, acylamino, cyano, hydroxy, halo, mercapto, nitro, carboxaldehyde, carboxy, alkoxycarbonyl and carboxamide. More specifically, the substituents may be F, Cl, Br, I, OH, NO₂, CN, C(O)-C₁₋₆ alkyl, C(O)-aryl, C(O)-heteroaryl, CO₂-alkyl, CO₂-aryl, CO₂-heteroaryl, CONH₂, CONH-C₁₋₆ alkyl, CONH-aryl, CONH-heteroaryl, OC(O)-C₁₋₆ alkyl, OC(O)-aryl, OC(O)-heteroaryl, OCO₂-alkyl, OCO₂-aryl, OCO₂-heteroaryl, OCONH₂, OCONH-C₁₋₆ alkyl, OCONH-aryl, OCONH-heteroaryl, NHC(O)-C₁₋₆ alkyl, NHC(O)-aryl, NHC(O)-heteroaryl, NHCO₂-alkyl, NHCO₂-aryl, NHCO₂-heteroaryl, NHCONH₂, NHCONH-C₁₋₆ alkyl, NHCONH-aryl, NHCONH-heteroaryl, SO₂-C₁₋₆ alkyl, SO₂-aryl, SO₂-heteroaryl, SO₂NH₂, SO₂NH-C₁₋₆ alkyl, SO₂NH-aryl, SO₂NH-heteroaryl, C₁₋₆ alkyl, C₃₋₆ cycloalkyl, CF₃, CH₂CF₃, CHCl₂, CH₂OH, CH₂CH₂OH, CH₂NH₂, CH₂SO₂CH₃, aryl, heteroaryl, benzyl, benzyloxy, aryloxy, heteroaryloxy, C₁₋₆ alkoxy, methoxymethoxy, methoxyethoxy, amino, benzylamino, arylamino, heteroarylamino, C₁₋₃ alkylamino, thio, aryl-thio, heteroarylthio, benzyl-thio, C₁₋₆ alkyl-thio, or methylthiomethyl. In addition, substituted aryl groups include tetrafluorophenyl and pentafluorophenyl.

The term "arylalkyl group" refers to an aryl group attached to an alkyl group. An example of an arylalkyl group is a benzyl group.

The term "substituted arylalkyl group" refers to an aryl group or substituted aryl group attached to an alkyl group or a substituted alkyl group, provided that one or both of the aryl and alkyl groups are substituted.

The term "heteroaryl" refers to a cyclic aromatic radical having from five to ten ring atoms of which one ring atom is selected from S, O and N; zero, one, two, or three ring atoms are additional heteroatoms independently selected from S, O and N; and the remaining ring atoms are carbon, the radical being joined to the rest of the molecule via any of the ring atoms, such as, for example, pyridinyl, pyrazinyl, pyrimidinyl, pyrrolyl, pyrazolyl, imidazolyl, triazolyl,

tetrazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, thiadiazolyl, oxadiazolyl, thiophenyl, furanyl, quinolinyl, isoquinolinyl, and the like.

The term "substituted heteroaryl" refers to a heteroaryl group as defined herein, substituted by independent replacement of one, two, three, four, or five of the hydrogen atoms thereon with F, Cl, Br, I, OH, NO₂, CN, C(O)-C₁₋₆ alkyl, C(O)-aryl, C(O)-heteroaryl, CO₂-alkyl, CO₂-aryl, CO₂-heteroaryl, CONH₂, CONH-C₁₋₆ alkyl, CONH-aryl, CONH-heteroaryl, OC(O)-C₁₋₆ alkyl, OC(O)-aryl, OC(O)-heteroaryl, OCO₂-alkyl, OCO₂-aryl, OCO₂-heteroaryl, OCONH₂, OCONH-C₁₋₆ alkyl, OCONH-aryl, OCONH-heteroaryl, NHC(O)-C₁₋₆ alkyl, NHC(O)-aryl, NHC(O)-heteroaryl, NHCO₂-alkyl, NHCO₂-aryl, NHCO₂-heteroaryl, NHCONH₂, NHCONH-C₁₋₆ alkyl, NHCONH-aryl, NHCONH-heteroaryl, SO₂-C₁₋₆ alkyl, SO₂-aryl, SO₂-heteroaryl, SO₂NH₂, SO₂NH-C₁₋₆ alkyl, SO₂NH-aryl, SO₂NH-heteroaryl, C₁₋₆ alkyl, C₃₋₆ cycloalkyl, CF₃, CH₂CF₃, CHCl₂, CH₂OH, CH₂CH₂OH, CH₂NH₂, CH₂SO₂CH₃, aryl, heteroaryl, benzyl, benzyloxy, aryloxy, heteroaryloxy, C₁₋₆ alkoxy, methoxymethoxy, methoxyethoxy, amino, benzylamino, arylamino, heteroarylamino, C₁₋₃ alkylamino, thio, aryl-thio, heteroarylthio, benzyl-thio, C₁₋₆ alkyl-thio, or methylthiomethyl.

The term "heterocyclic" refers to heterocycloalkyl and heteroaryl. The term "substituted heterocyclic," as used herein, refers to substituted heterocycloalkyl and substituted heteroaryl.

The term "macrolide" refers to any compound possessing a 14- or 15- macrocyclic ring, and derivatives thereof (such as keto, oxime, cyclic carbonate derivatives). These include, for example, compounds that are (or are synthetically derived from) known antibacterial agents including, but not limited to, erythromycin, clarithromycin, azithromycin, telithromycin, roxithromycin, pikromycin, flurithromycin, and dirithromycin.

In the formulas herein, a broken or dashed circle within a ring indicates that the ring is either aromatic or non-aromatic. A bond extending from a chemical moiety that is depicted as crossing a bond in a ring, but is not attached directly to a ring atom, indicates that the chemical moiety may be bonded to any atom of the ring. As to any of the above chemical moieties that contain one or more substituents, it is understood that such moieties do not contain any substitution or substitution patterns that are sterically impractical and/or synthetically unfeasible. In addition, the compounds of this invention include all stereochemical isomers arising from the substitution of these moieties.

The term "pharmaceutically acceptable salt" refers to those salts which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well

5 known in the art. For example, S. M. Berge, *et al.* describe pharmaceutically acceptable salts in detail in J. PHARM SCIENCES 66: 1-19 (1977). The salts can be prepared *in situ* during the final isolation and purification of the compounds of the invention, or separately by reacting the free base function with a suitable organic acid. Examples of pharmaceutically acceptable, nontoxic acid addition salts are salts of an amino group formed with inorganic acids (such as
10 hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid and perchloric acid), or with organic acids (such as acetic acid, oxalic acid, maleic acid, tartaric acid, citric acid, succinic acid or malonic acid), or by using other methods used in the art (such as ion exchange). Other pharmaceutically acceptable salts include adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate,
15 cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate,
20 propionate, stearate, succinate, sulfate, tartrate, thiocyanate, p-toluenesulfonate, undecanoate, valerate salts, and the like. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, and the like. Further pharmaceutically acceptable salts include, when appropriate, nontoxic ammonium, quaternary ammonium, and amine cations formed using counterions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate,
25 loweralkyl sulfonate and aryl sulfonate.

The term "pharmaceutically acceptable ester" refers to esters that hydrolyze *in vivo* and include those that break down readily in the human body to leave the parent compound or a salt thereof. Suitable ester groups include, for example, those derived from pharmaceutically acceptable aliphatic carboxylic acids, particularly alkanoic, alkenoic, cycloalkanoic and
30 alkanedioic acids, in which each alkyl or alkenyl moiety advantageously has not more than 6 carbon atoms. Other suitable ester groups include, for example, those derived from

pharmaceutically acceptable alcohols, such as stright-chain or branched aliphatic alcohols, benzylic alcohols, and amino-alcohols. Examples of particular esters include formates, acetates, propionates, butyrates, acrylates, ethylsuccinates, and methyl, ethyl, propyl, benzyl, and 2-aminoethyl alcohol esters.

5 The term "pharmaceutically acceptable prodrugs" refers to those prodrugs of the compounds of the present invention which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals with undue toxicity, irritation, allergic response, and the like, commensurate with a reasonable benefit/risk ratio, and effective for their intended use, as well as the zwitterionic forms, where possible, of the
10 compounds of the invention. The term "prodrug" refers to compounds that are rapidly transformed *in vivo* to yield the parent compound of the previously formula, for example by hydrolysis in blood. A thorough discussion is provided in T. Higuchi and V. Stella, Pro-drugs as Novel Delivery Systems, Vol. 14 of the A. C. S. Symposium Series, and in Edward B. Roche, ed., Bioreversible Carriers in Drug Design, American Pharmaceutical Association and Pergamon
15 Press, 1987.

 The term "physiologically acceptable cation" refers to common, positively charged species such as (but not limited to) metals such as sodium, potassium, calcium, magnesium, zinc and the like. The cation can also be an organic species such as an amine salt. Non-limiting examples of such amine salts can be the protonated form of methylamine, ethylamine,
20 cyclohexylamine, lysine, N-methylglucamine, diethanolamine, triethanolamine, tris-(hydroxymethyl)aminomethane, piperidine, morpholine, and the like.

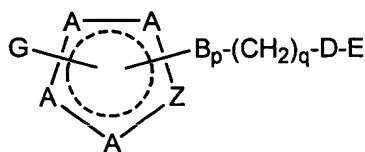
 The term "electron-withdrawing group" refers to groups well known to those in the art capable of pulling electron density towards the group and away from a source (such as an aromatic ring, an olefin, a carbonyl-like group or a sigma bond between two designated atoms).
25 Examples of such electron-withdrawing groups are, for example, nitro, keto, formyl, acyl, halogens, carboxy, trihaloalkyl, sulfonyl and the like.

 Throughout the description, where compositions are described as having, including, or comprising specific components, or where processes are described as having, including, or comprising specific process steps, it is contemplated that compositions of the present invention
30 also consist essentially of, or consist of, the recited components, and that the processes of the present invention also consist essentially of, or consist of, the recited processing steps. Further,

it should be understood that the order of steps or order for performing certain actions are immaterial so long as the invention remains operable. Moreover, two or more steps or actions may be conducted simultaneously.

5 2. Compounds of the Invention

In one aspect, the invention provides compounds having the formula:



or a pharmaceutically acceptable salt, ester, or prodrug thereof,

wherein

10 A, at each occurrence, independently is carbon, carbonyl, or nitrogen, provided at least one A is carbon;

Z is carbon, nitrogen, oxygen, or sulfur;

B is selected from the group consisting of O, NR^2 , S(O)_r , C=O , C=S , and C=NOR^3 ,
p is 0 or 1;

15 q, at each occurrence, independently is 0 or 1;

r is 0, 1, or 2;

R^2 , at each occurrence, independently is selected from the group consisting of:

a) hydrogen, b) $\text{S(O)}_r\text{R}^4$, c) formyl, d) C_{1-8} alkyl, e) C_{2-8} alkenyl, f) C_{2-8} alkynyl,
g) C_{1-8} alkoxy, h) C_{1-8} alkylthio, i) C_{1-8} acyl, j) saturated, unsaturated, or aromatic
20 C_{3-8} carbocycle, and k) saturated, unsaturated, or aromatic 5-10 membered
heterocycle containing one or more heteroatoms selected from the group
consisting of nitrogen, oxygen, and sulfur,

wherein any of d) – k) optionally is substituted with one or more moieties
selected from the group consisting of carbonyl, aryl, substituted aryl,
25 heteroaryl, substituted heteroaryl, F, Cl, Br, I, CN, NO_2 , $-\text{NR}^3\text{R}^3$, $-\text{OR}^3$,
 $-\text{S(O)}_r\text{R}^4$, $-\text{S(O)}_r\text{NR}^3\text{R}^3$, $-\text{C(O)}\text{R}^3$, $-\text{C(O)}\text{OR}^3$, $-\text{OC(O)}\text{R}^3$, $-\text{C(O)}\text{NR}^3\text{R}^3$, and
 $-\text{OC(O)}\text{NR}^3\text{R}^3$;

alternatively, two R^2 groups, taken together with the atom to which they are bonded, form i) 5-8 membered saturated or unsaturated carbocycle, or ii) 5-8 membered saturated or unsaturated heterocycle containing one or more atoms selected from the group consisting of nitrogen, oxygen, and sulfur,

5 wherein i) – ii) optionally is substituted with one or more moieties selected from the group consisting of carbonyl, F, Cl, Br, I, CN, NO_2 , $-NR^3R^3$, $-OR^3$, $-S(O)_rR^4$, $-S(O)_rNR^3R^3$, $-C(O)R^3$, $-C(O)OR^3$, $-OC(O)R^3$, $-C(O)NR^3R^3$, $-OC(O)NR^3R^3$, C_{1-6} acyl, aryl, substituted aryl, heteroaryl, and substituted heteroaryl;

R^3 , at each occurrence, independently is selected from the group consisting of:

10 a) hydrogen, b) C_{1-8} alkyl, c) C_{2-8} alkenyl, d) C_{2-8} alkynyl, e) C_{1-8} acyl, f) saturated, unsaturated, or aromatic C_{3-8} carbocycle, and g) saturated, unsaturated, or aromatic 5-10 membered heterocycle containing one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur, wherein any of b) – h) optionally is substituted with one or more moieties
15 selected from the group consisting of carbonyl, F, Cl, Br, I, CN, NO_2 , $-NR^6R^6$, $-OR^6$, $-S(O)_rR^6$, $-S(O)_rNR^6R^6$, $-C(O)R^6$, $-C(O)OR^6$, $-OC(O)R^6$, $-C(O)NR^6R^6$, $-OC(O)NR^6R^6$, C_{1-6} acyl, aryl, substituted aryl, heteroaryl, and substituted heteroaryl;

alternatively, two R^3 groups, taken together with the atom to which they are bonded, form

20 i) a 5-7 membered saturated or unsaturated carbocycle, or ii) a 5-7 membered saturated or unsaturated heterocycle containing one or more atoms selected from the group consisting of nitrogen, oxygen, and sulfur,

 wherein i) - ii) optionally is substituted with one or more moieties selected from the group consisting of carbonyl, F, Cl, Br, I, CN, NO_2 , $-NR^6R^6$, $-OR^6$, $-S(O)_rR^6$,
25 $-S(O)_rNR^6R^6$, $-C(O)R^6$, $-C(O)OR^6$, $-OC(O)R^6$, $-C(O)NR^6R^6$, $-OC(O)NR^6R^6$, C_{1-6} acyl, aryl, substituted aryl, heteroaryl, and substituted heteroaryl;

R^4 is selected from the group consisting of:

 a) hydrogen, b) $-NR^3R^3$, c) $-NR^3OR^3$, d) $-NR^3NR^3R^3$ e) $-NHC(O)R^3$,
30 f) $-C(O)NR^3R^3$, g) $-N_3$, h) C_{1-8} alkyl, i) C_{2-8} alkenyl, j) C_{2-8} alkynyl, k) saturated, unsaturated, or aromatic C_{3-8} carbocycle, and l) saturated, unsaturated, or aromatic

5-10 membered heterocycle containing one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur,

wherein any of h) – l) optionally is substituted with one or more moieties selected from the group consisting of carbonyl, F, Cl, Br, I, CN, NO₂,
5 -NR³R³, -OR³, -SR³, -S(O)_rR⁵, -S(O)_rNR³R³, -C(O)R³, -C(O)OR³,
-OC(O)R³, -C(O)NR³R³, -OC(O)NR³R³, C₁₋₆ alkyl, C₁₋₆ alkenyl,
C₁₋₆ alkynyl, C₁₋₆ acyl, aryl, substituted aryl, heteroaryl, and substituted heteroaryl;

R⁵ is selected from the group consisting of:

10 a) hydrogen, b) -NR³R³, c) -NR³OR³, d) -NR³NR³R³ e) -NHC(O)R³,
f) -C(O)NR³R³, g) -N₃, h) C₁₋₈ alkyl, i) C₂₋₈ alkenyl, j) C₂₋₈ alkynyl, k) saturated,
unsaturated, or aromatic C₃₋₈ carbocycle, and l) saturated, unsaturated, or aromatic
5-10 membered heterocycle containing one or more heteroatoms selected from the
group consisting of nitrogen, oxygen, and sulfur,

15 wherein any of h) – l) optionally is substituted with one or more moieties
selected from the group consisting of F, Cl, Br, I, CN, NO₂, -NR³R³, -OR³,
-SR³-C(O)R³, -C(O)OR³, -OC(O)R³, -C(O)NR³R³, -OC(O)NR³R³,
C₁₋₆ alkyl, C₁₋₆ alkenyl, C₁₋₆ alkynyl, C₁₋₆ acyl, aryl, substituted aryl,
heteroaryl, and substituted heteroaryl; and

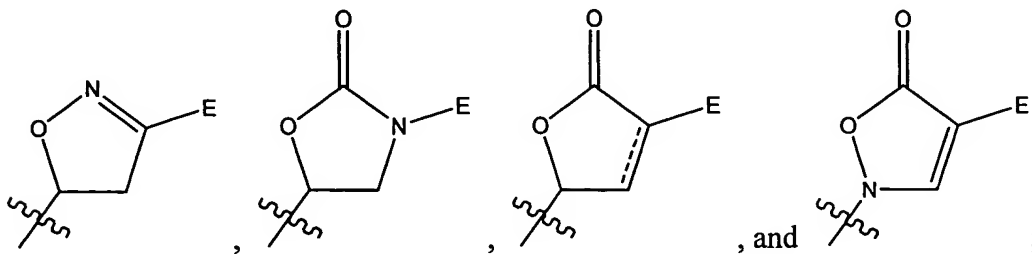
20 R⁶, at each occurrence, independently is selected from the group consisting of:

hydrogen, C₁₋₆ alkyl, C₁₋₆ alkenyl, C₁₋₆ alkynyl, C₁₋₆ acyl, aryl, substituted aryl,
heteroaryl, substituted heteroaryl;

alternatively, two R⁶ groups taken together are -(CH₂)_s-,

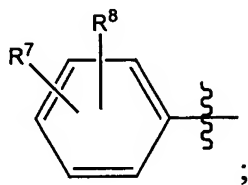
wherein s is 1, 2, 3, 4, or 5;

25 D-E is selected from the group consisting of:



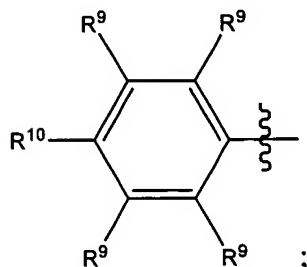
E is selected from the group consisting of:

a)

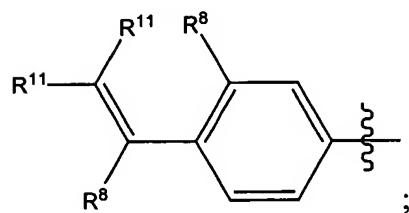


5

b)



c)



d) 5-10 membered saturated, unsaturated, or aromatic heterocycle containing one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur, and optionally substituted with one or more R^{13} groups;

e) C_{5-10} saturated, unsaturated, or aromatic carbocycle, optionally substituted with one or more R^{13} groups;

f) C_{1-8} alkyl,

15

g) C_{2-8} alkenyl,

h) C_{3-8} alkynyl,

i) C_{1-8} alkoxy,

j) C_{1-8} alkylthio,

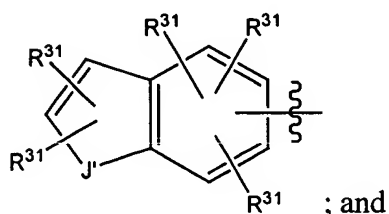
k) C_{1-8} acyl,

l) $S(O)_rR^5$; and

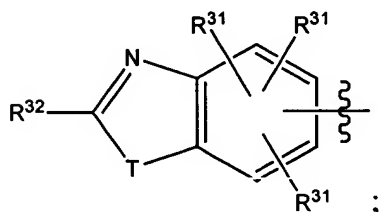
m) hydrogen,

n) a β -carbolin-3-yl, or indolizinyll bonded via the 6-membered ring, wherein the β -carbolin-3-yl, or indolizinyll optionally is substituted with one to three R^{30} groups;

5 o)



p)



wherein any of f) – k) optionally is substituted with

- 10 i) one or more R^{13} groups;
- ii) 5-6 membered saturated, unsaturated, or aromatic heterocycle containing one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur, and optionally substituted with one or more R^{13} groups; or
- 15 iii) C_{5-10} saturated, unsaturated, or aromatic carbocycle, optionally substituted with one or more R^{13} groups;

R^7 is selected from the group consisting of:

- a) hydrogen, b) carbonyl, c) formyl, d) F, e) Cl, f) Br, g) I, h) CN, i) NO_2 , j) OR^3 ,
k) $-S(O)_rR^5$, l) $-S(O)_iN=R^2$, m) $-C(O)R^2$, n) $-C(O)OR^3$, o) $-OC(O)R^2$,
20 p) $-C(O)NR^2R^2$, q) $-OC(O)NR^2R^2$, r) $-C(=NR^{12})R^2$, s) $-C(R^2)(R^2)OR^3$,
t) $-C(R^2)(R^2)OC(O)R^2$, u) $-C(R^2)(OR^3)(CH_2)_rNR^2R^2$, v) $-NR^2R^2$, w) $-NR^2OR^3$,
x) $-N(R^2)C(O)R^2$, y) $-N(R^2)C(O)OR^3$, z) $-N(R^2)C(O)NR^2R^2$, aa) $-N(R^2)S(O)_rR^5$,
bb) $-C(OR^6)(OR^6)R^2$, cc) $-C(R^2)(R^3)NR^2R^2$, dd) $-C(R^2)(R^3)NR^2R^{12}$, ee) $=NR^{12}$,

ff) $-C(S)NR^2R^2$, gg) $-N(R^2)C(S)R^2$, hh) $-OC(S)NR^2R^2$, ii) $-N(R^2)C(S)OR^3$,
 jj) $-N(R^2)C(S)NR^2R^2$, kk) $-SC(O)R^2$, ll) C_{1-8} alkyl, mm) C_{2-8} alkenyl,
 nn) C_{2-8} alkynyl, oo) C_{1-8} alkoxy, pp) C_{1-8} alkylthio, qq) C_{1-8} acyl, rr) saturated,
 5 unsaturated, or aromatic C_{5-10} carbocycle, and ss) saturated, unsaturated, or
 aromatic 5-10 membered heterocycle containing one or more heteroatoms
 selected from the group consisting of nitrogen, oxygen, and sulfur,

wherein any of ll) – ss) optionally is substituted with one or more moieties
 selected from the group consisting of:

carbonyl; formyl; F; Cl; Br; I; CN; NO_2 ; OR^3 ; $-S(O)_rR^5$; $-S(O)_rN=R^2$,
 10 $-C(O)R^2$; $-C(O)OR^3$; $-OC(O)R^2$; $-C(O)NR^2R^2$; $-OC(O)NR^2R^2$;
 $-C(=NR^{10})R^2$; $-C(R^2)(R^2)OR^3$; $-C(R^2)(R^2)OC(O)R^2$;
 $-C(R^2)(OR^3)(CH_2)_rNR^2R^2$; $-NR^2R^2$; $-NR^2OR^3$; $-NR^2C(O)R^2$;
 $-NR^2C(O)OR^3$; $-NR^2C(O)NR^2R^2$; $-NR^2S(O)_rR^5$; $-C(OR^6)(OR^6)R^2$;
 $-C(R^2)(R^3)NR^2R^2$; $-C(R^2)(R^3)NR^2R^{12}$; $=NR^{12}$; $-C(S)NR^2R^2$; $-NR^2C(S)R^2$;
 15 $-OC(S)NR^2R^2$; $-NR^2C(S)OR^3$; $-NR^2C(S)NR^2R^2$; $-SC(O)R^2$; C_{2-5} alkenyl;
 C_{2-5} alkynyl; C_{1-8} alkoxy; C_{1-8} alkylthio; C_{1-8} acyl; saturated, unsaturated,
 or aromatic C_{5-10} carbocycle, optionally substituted with one or more R^8
 groups; and saturated, unsaturated, or aromatic 5-10 membered
 heterocycle containing one or more heteroatoms selected from the group
 20 consisting of nitrogen, oxygen, and sulfur, and optionally substituted with
 one or more R^8 groups;

R^8 is selected from the group consisting of:

hydrogen; F; Cl; Br; I; CN; NO_2 ; OR^6 ; aryl; substituted aryl; heteroaryl;
 substituted heteroaryl; and C_{1-6} alkyl, optionally substituted with one or more
 25 moieties selected from the group consisting of aryl, substituted aryl, heteroaryl,
 substituted heteroaryl, F, Cl, Br, I, CN, NO_2 , and OR^6 ;

alternatively, R^7 and R^8 taken together are $-O(CH_2)_rO-$;

R^9 , at each occurrence, independently is selected from the group consisting of:

hydrogen, F, Cl, Br, I, CN, OR^3 , NO_2 , $-NR^2R^2$, C_{1-6} alkyl, C_{1-6} acyl, and
 30 C_{1-6} alkoxy;

R^{10} is selected from the group consisting of:

a) saturated, unsaturated, or aromatic C₅₋₁₀ carbocycle,

b) saturated, unsaturated, or aromatic 5-10 membered heterocycle containing one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur,

5 c) -X-C₁₋₆ alkyl-saturated, unsaturated, or aromatic 5-10 membered heterocycle containing one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur,

wherein X is O or NR³,

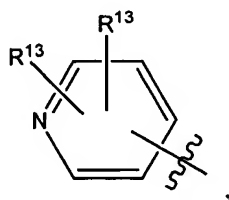
10 d) saturated, unsaturated, or aromatic 10-membered bicyclic ring system optionally containing one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur,

e) saturated, unsaturated, or aromatic 13-membered tricyclic ring system optionally containing one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur,

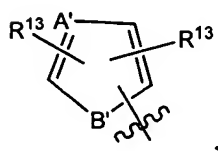
f)



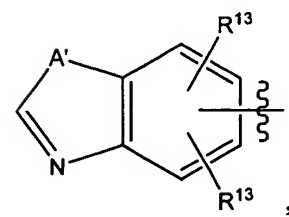
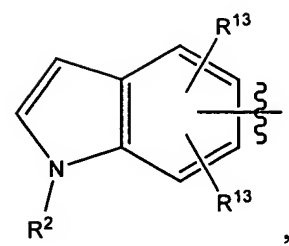
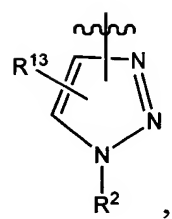
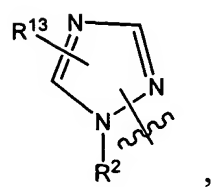
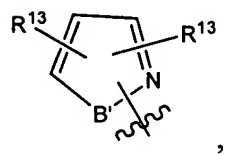
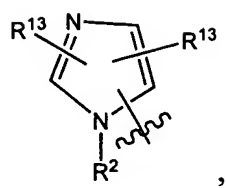
g)



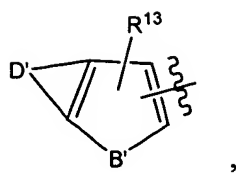
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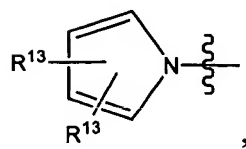
20 i)



o)

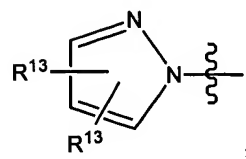


p)

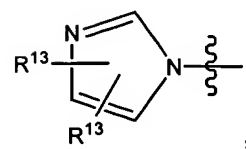


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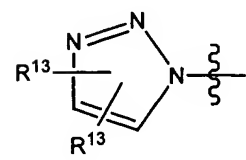
q)



r)

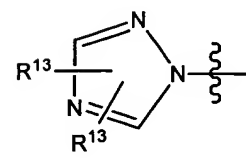


s)

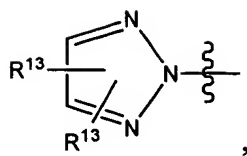


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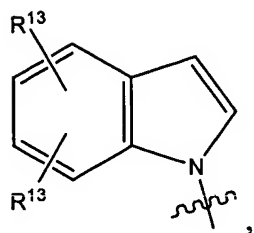
t)



u)



v)



w) a diazinyl group,

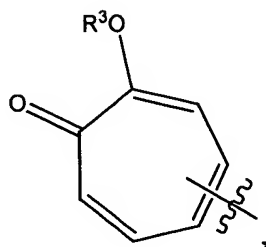
x) a triazinyl group,

y) a quinolinyl group,

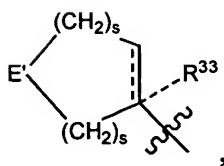
z) a quinoxaliny group,

aa) a naphthyridinyl group,

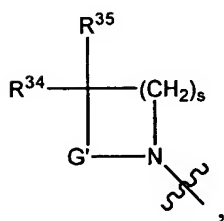
bb)



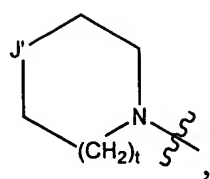
cc)



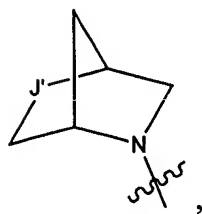
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ee)

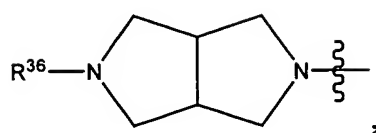


ff)

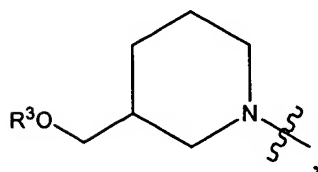


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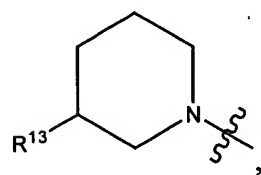
gg)



hh)

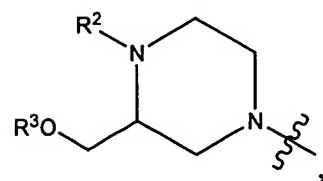


ii)

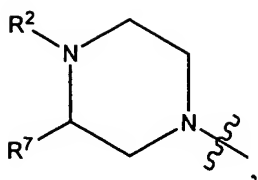


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jj)



kk)

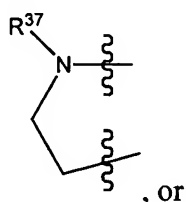


ll) $-\text{C}(\text{O})\text{CH}_3$, and

mm) R^9 ,

wherein any of a) – kk) optionally is substituted with one or more R^{13} groups;

5 alternatively, R^{10} and one R^9 group taken together is



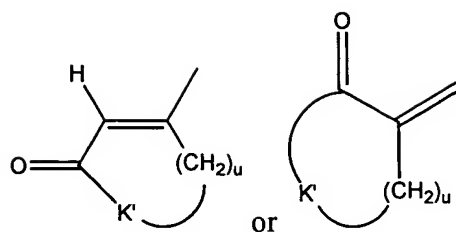
alternatively, R^{10} and one R^9 group, taken together with the atoms to which they are bonded, form a 5-7 membered saturated or unsaturated carbocycle, optionally substituted with one or more R^{13} groups; or a 5-7 membered saturated or unsaturated heterocycle containing one or more atoms selected from the group consisting of nitrogen, oxygen, and sulfur, and optionally substituted with one or more R^{13} groups;

R^{11} at each occurrence, independently is selected from the group consisting of:

hydrogen; an electron-withdrawing group; aryl; substituted aryl; heteroaryl; substituted heteroaryl; and C_{1-6} alkyl, optionally substituted with F, Cl, or Br;

15 alternatively, any R^{11} and R^8 , taken together with the atoms to which they are bonded, form a 5-7 membered saturated or unsaturated carbocycle, optionally substituted with one or more R^{13} groups; or a 5-7 membered saturated or unsaturated heterocycle containing one or more atoms selected from the group consisting of nitrogen, oxygen, and sulfur, and optionally substituted with one or more R^{13} groups;

20 alternatively, any R^{11} and R^8 , taken together with the atoms to which they are bonded, form $-(\text{CH}_2)_k-$ or a 5-, 6-, or 7-membered ring having the formula:



wherein

u is 2, 3, 4, or 5;

R¹² is selected from the group consisting of:

-NR²R², -OR³, -OC(O)R², -OC(O)OR³, -NR²C(O)R², -NR²C(O)NR²R²,
-NR²C(S)NR²R², and -NR²C(=NR²)NR²R²;

R¹³, at each occurrence, independently is selected from the group consisting of:

a) hydrogen, b) carbonyl, c) formyl d) F, e) Cl, f) Br, g) I, h) CN, i) NO₂, j) OR³,
k) -S(O)_rR⁵, l) -S(O)_rN=R³, m) -C(O)R², n) -C(O)OR³, o) -OC(O)R²,
p) -C(O)NR²R², q) -OC(O)NR²R², r) -C(=NR¹²)R², s) -C(R²)(R²)OR³,
t) -C(R²)(R²)OC(O)R², u) -C(R²)(OR³)(CH₂)_rNR²R², v) -NR²R², w) -NR²OR³,
x) -N(R²)C(O)R², y) -N(R²)C(O)OR³, z) -N(R²)C(O)NR²R², aa) -N(R²)S(O)_rR⁵,
bb) -C(OR⁶)(OR⁶)R², cc) -C(R²)(R³)NR²R², dd) -C(R²)(R³)NR²R¹², ee) =NR¹²,
ff) -C(S)NR²R², gg) -N(R²)C(S)R², hh) -OC(S)NR²R², ii) -N(R²)C(S)OR³,
jj) -N(R²)C(S)NR²R², kk) -SC(O)R², ll) C₁₋₈ alkyl, mm) C₂₋₈ alkenyl,

nn) C₂₋₈ alkynyl, oo) C₁₋₈ alkoxy, pp) C₁₋₈ alkylthio, qq) C₁₋₈ acyl, rr) saturated,
unsaturated, or aromatic C₅₋₁₀ carbocycle, ss) saturated, unsaturated, or aromatic
5-10 membered heterocycle containing one or more heteroatoms selected from the
group consisting of nitrogen, oxygen, and sulfur, tt) saturated, unsaturated, or
aromatic 10-membered bicyclic ring system optionally containing one or more
heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur,
and uu) saturated, unsaturated, or aromatic 13-membered tricyclic ring system
optionally containing one or more heteroatoms selected from the group consisting
of nitrogen, oxygen, and sulfur,

wherein any of ll) – uu) optionally is substituted with one or more
moieties selected from the group consisting of:

carbonyl; formyl; F; Cl; Br; I; CN; NO₂; OR³; -S(O)_rR⁵; -S(O)_rN=R²,
 -C(O)R²; -C(O)OR³; -OC(O)R²; -C(O)NR²R²; -OC(O)NR²R²;
 -C(=NR¹²)R²; -C(R²)(R²)OR³; -C(R²)(R²)OC(O)R²;
 -C(R²)(OR³)(CH₂)_rNR²R²; -NR²R²; -NR²OR³; -NR²C(O)R²;
 -NR²C(O)OR³; -NR²C(O)NR²R²; -NR²S(O)_rR⁵; -C(OR⁶)(OR⁶)R²;
 -C(R²)(R³)NR²R²; -C(R²)(R³)NR²R¹²; =NR¹²; -C(S)NR²R²; -NR²C(S)R²;
 -OC(S)NR²R²; -NR²C(S)OR³; -NR²C(S)NR²R²; -SC(O)R²; C₁₋₈ alkyl,
 C₂₋₈ alkenyl; C₂₋₈ alkynyl; C₁₋₈ alkoxy; C₁₋₈ alkylthio; C₁₋₈ acyl; saturated,
 unsaturated, or aromatic C₃₋₁₀ carbocycle optionally substituted with one
 or more R⁷ groups; and saturated, unsaturated, or aromatic 3-10 membered
 heterocycle containing one or more heteroatoms selected from the group
 consisting of nitrogen, oxygen, and sulfur, and substituted with one or
 more R⁷ groups;

A' is CH, N, S, or O;

B' is O, S, or NR²;

D' is an unsaturated 4-atom linker containing one nitrogen atom and three carbon atoms,
 which forms a pyridyl ring fused with the heteroaryl moiety;

E' is O, NR⁵¹, or S(O)_r;

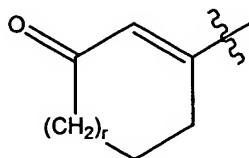
G' is -CH₂-, -CH₂CH₂-, -CH₂(OH)CH₂-, -C(O)-, or -CH₂CH₂CH₂-;

J' is -S(O)_r-, -O-, or -NR³⁶-;

K' is CH₂, O, S, or NR²;

R³⁰ is selected from the group consisting of:

- a) carbonyl, b) formyl, c) F, d) Cl, e) Br, f) CN, g) -OR³, h) -SR³, i) -CF₃,
- j) -NO₂, k) -NR²R², l) -NR³⁸R³⁸, m)



n) C₁₋₆ alkyl, o) C₂₋₆ alkenyl, p) C₂₋₆ alkynyl, q) C₁₋₆ alkoxy, r) -C(O)-C₁₋₆ alkyl, s) C₁₋₆ alkylthio, t) C₁₋₆ acyl, u) C₂₋₈ alkenylphenyl, v) aryl, and w) heteroaryl,

wherein any of n) – w) optionally is substituted with one or more R³⁹ groups;

5 R³¹, at each occurrence, independently is selected from the group consisting of:

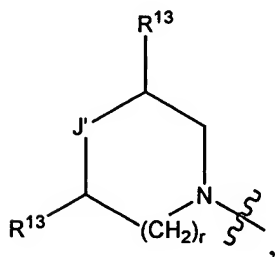
a) hydrogen, b) carbonyl, c) F, d) Cl, e) Br, f) -CN, g) formyl, h) -NO₂, i) -OR³, j) -NR²R², k) aryl, l) substituted aryl, m) heteroaryl, n) substituted aryl, o) C₁₋₆ alkyl, p) C₂₋₆ alkenyl, q) C₂₋₆ alkynyl, r) C₁₋₆ alkylthio, s) C₁₋₆ acyl, t) C₁₋₆ alkoxy, and u) -C(O)C₁₋₆ alkoxy,

10 wherein any of o) – u) optionally is substituted with one or more moieties from the group consisting of:

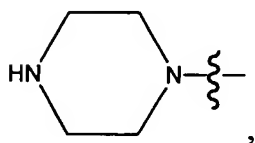
-N(phenyl)(CH₂CH₂OH), -OCH(CH₃)(OCH₂CH₃),
-O-phenyl-[para-NHC(O)CH₃], and R¹³;

R³², at each occurrence, independently is selected from the group consisting of:

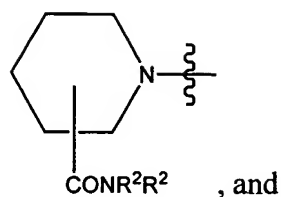
15 a) hydrogen, b) carbonyl, c) formyl, d) -OR⁴³, e) -NR⁴⁴R⁴⁴, f) -S(O)_rR⁴⁷, g) -S(O)_rNR⁴⁴R⁴⁴, h) aryl, i) substituted aryl, j) heteroaryl, k) substituted heteroaryl, l) C₁₋₆ alkyl, m) C₂₋₆ alkenyl, n) C₂₋₆ alkynyl, o) C₁₋₆ alkylthio, p) C₁₋₆ acyl, q) C₁₋₆ alkoxy, r) -C(O)-C₁₋₆ alkoxy, s)



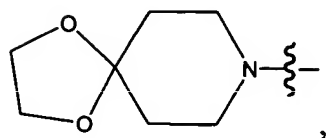
t)



u)



v)



5 wherein any of n) – w) optionally is substituted with one or more moieties from the group consisting of:

-N(phenyl)(CH₂CH₂OH), -OCH(CH₃)(OCH₂CH₃),
-O-phenyl-[para-NHC(O)CH₃] and R¹³;

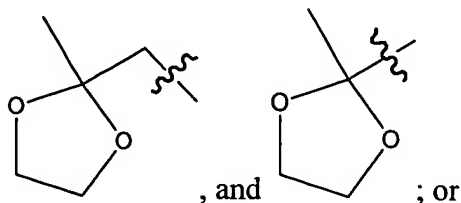
R³³ is hydrogen, F, Cl, Br, C₁₋₆ alkyl, or C₁₋₆ alkyl-aryl;

10 R³⁴ is hydrogen or CH₃;

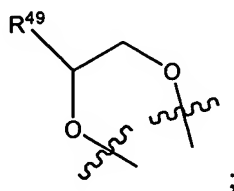
R³⁵ is selected from the group consisting of:

hydrogen, -OH, -CH₃, -OCH₃, -NHC(O)OR², -NHC(O)CH₂OR³,
-C(O)O-C₁₋₆ alkyl, -CH₂OH, -NHCH₃, -C(O)O-C₁₋₆ alkyl, -C(O)CH₃,
-CH₂C(O)CH₃,

15

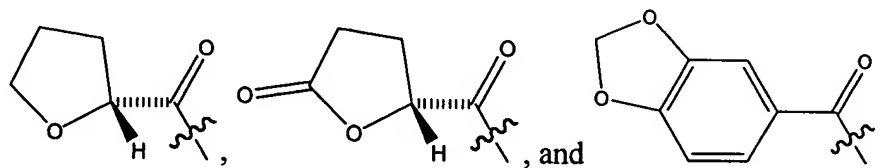


alternatively, R³⁴ and R³⁵ taken together are a carbonyl, =NR⁴⁸, or



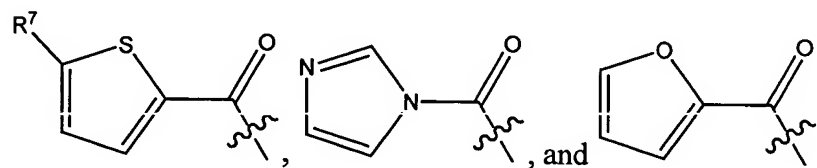
R³⁶ is selected from the group consisting of:

-C(O)OR³, -C(O)C(R⁵⁰)(R⁵⁰)(OR³), -C(O)R², -SO₂R⁴, -C(O)(CH₂)₂C(O)CH₃,
 -C(O)CH₂OH, -(CH₂)₂R², -C(O)CH₂OC(O)R², -CH₂CN, -CH₂CHF₂, -SO₂NR²R²,
 -NHC(O)CH₂N(CH₃)₂,



R³⁷ is selected from the group consisting of:

-C(O)CH₃, -C(O)H, -C(O)CHCl₂, -C(O)CH₂OH, -SO₂CH₃,
 -C(O)CH₂OC(O)CH₃, -C(O)CHF₂, -C(O)CH₂OC(O)H, -C(O)CH₂OCH₂-C≡CH,
 -C(O)CH₂OCH₂C₆H₅,



R³⁸, at each occurrence, independently is selected from the group consisting of:

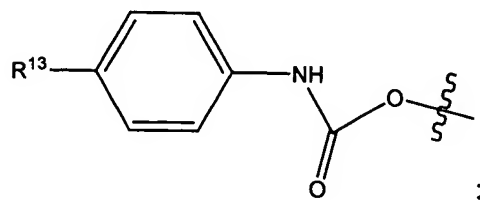
hydrogen, formyl, C₁₋₄ alkyl, C₁₋₄ acyl, aryl, C₃₋₆ cycloalkyl, -P(O)(OR³)(OR³),
 and -SO₂R⁴;

15 alternatively, two R³⁸ groups taken together with the atom to which they are bonded form a 5- or 6-membered saturated heterocyclic group containing one or more atoms selected from the group consisting of nitrogen, oxygen, and sulfur, and optionally substituted with phenyl, pyrimidyl, C₁₋₃ alkyl, or C₁₋₃ acyl;

R³⁹ is selected from the group consisting of:

20 a) carbonyl, b) formyl, c) F, d) Cl, e) Br, f) I, g) CN, h) -OR³, i) -SR³, j) -CF₃,
 k) -NO₂, l) -NR²R², m) -C(O)NR²R², n) -NR²R², o) -NR²(SO₂R⁶),
 p) -SO₂NR²R², q) -S(O)_rR⁶, r) -CH=N-R⁴⁰, s) -CH(OH)-SO₃R⁴¹, t) C₁₋₆ alkyl,
 u) C₂₋₆ alkenyl, v) C₂₋₆ alkynyl, w) C₁₋₆ alkoxy, x) -C(O)-C₁₋₆ alkyl,
 y) C₁₋₆ alkylthio, z) C₁₋₆ acyl, aa) C₂₋₈ alkenylphenyl, bb) aryl, and cc) heteroaryl,

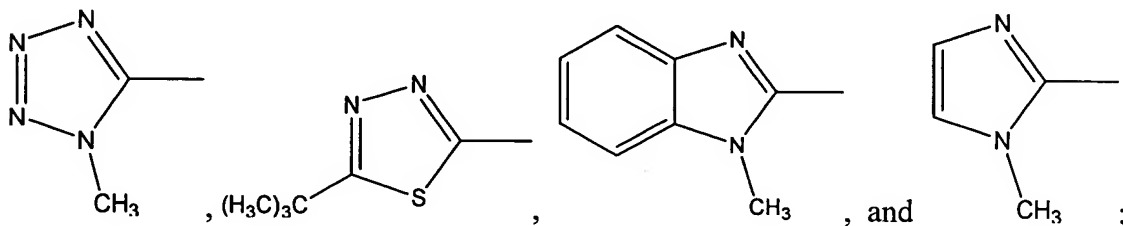
wherein any of s) – bb) optionally is substituted with -OH, -N₃,
C₁₋₅ alkoxy, C₁₋₅ acyl, -NR²R², -SR⁴², -OSO₂R⁶, or



R⁴⁰ is -OH, -OCH₂-aryl, -NHC(O)NH₂, -NHC(S)NH₂, or -NHC(=NH)NR²R²;

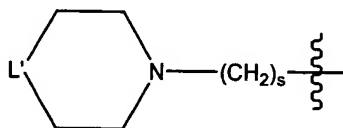
5 R⁴¹ is hydrogen or a sodium ion;

R⁴² is selected from the group consisting of:



R⁴³ is selected from the group consisting of:

a) C₁₋₈ alkyl, b) C₃₋₆ cycloalkyl, c) aryl, d) heteroaryl, e) pyridyl, and f)



10

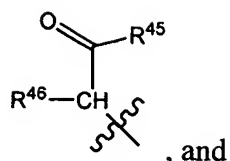
wherein

any of a) – f) optionally is substituted with one or more R¹³ groups, and

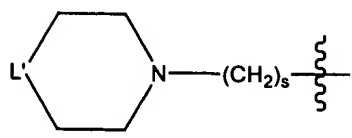
L' is O, CH₂, or NR²;

R⁴⁴, at each occurrence, independently is selected from the group consisting of:

15 a) hydrogen, b) C₃₋₆ cycloalkyl, c) C₁₋₆ acyl, d) C₁₋₈ alkyl, e) C₁₋₆ alkoxy,
f) heteroaryl, g) aryl,
h)

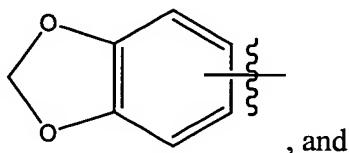


i)



wherein

5 any of b) – g) optionally is substituted with one or more R^{13} groups, or



L' is O, CH_2 , or NR^2 ;

R^{45} is -OH, C_{1-4} alkoxy, or $-NR^2R^2$;

10 R^{46} is hydrogen or a C_{1-8} alkyl group optionally substituted with one or moieties selected from the group consisting of indolyl, $-OR^3$, $-SR^3$, imidazolyl, C_{1-8} alkylthio, $-NR^2R^2$, and aryl, wherein the aryl group optionally is substituted with OH, $-C(O)NH_2$, $-CO_2H$, or $-C(=NH)NH_2$;

R^{47} is selected from the group consisting of:

a) C_{1-16} alkyl, b) C_{2-16} alkenyl, c) aryl, and d) heteroaryl,

15 wherein any of a) – d) optionally is substituted with one or more R^{13} groups;

R^{48} is selected from the group consisting of:

-OH, -OCH₃, -NH₂, -OC(O)OCH₃, -OC(O)CH₂OC(O)CH₃, -O(CH₂)₂OH, -OC(O)CH₂OCH₂C₆H₅, -O(CH₂)₂OCH₂OCH₃, and -OCH₂OCH₃;

20 R^{49} is selected from the group consisting of:

hydrogen, -CH₂OH, and -CH₂OCH₂OCH₃;

R⁵⁰, at each occurrence, independently is hydrogen or CH₃;

alternatively, two R⁵⁰ groups taken together with the carbon atom to which each is bonded are -CH₂CH₂-;

R⁵¹ is selected from the group consisting of:

- 5 a) hydrogen, b) C₁₋₆ alkyl, optionally substituted with one or more hydroxyl groups, halogens, or -CN, c) -(CH₂)_s-aryl, d) -CO₂R⁵², e) -COR⁵³,
f) -C(O)(CH₂)_sC(O)R⁵², g) -S(O)₂-C₁₋₆ alkyl, h) -S(O)₂(CH₂)_s-aryl, and
i) -(C(O))_s-Het;

R⁵² is selected from the group consisting of:

- 10 a) hydrogen, b) C₁₋₆ alkyl, optionally substituted with one or more hydroxyl groups, halogens, or -CN, c) -(CH₂)_s-aryl, and d) -(CH₂)_s-OR⁵⁴;

R⁵³ is selected from the group consisting of:

- a) C₁₋₆ alkyl, optionally substituted with one or more hydroxyl groups, halogens, or -CN, b) -(CH₂)_s-aryl, and c) -(CH₂)_s-OR⁵⁴;

- 15 R⁵⁴ is selected from the group consisting of:

- a) hydrogen, b) C₁₋₆ alkyl, c) -(CH₂)_s-aryl, and d) -C(O)-C₁₋₆ alkyl,

wherein the aryl group is selected from the group consisting of phenyl, pyridyl, and naphthyl,

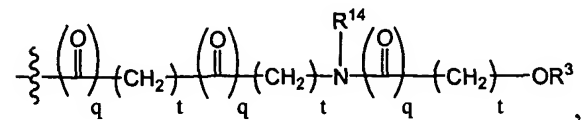
- 20 wherein each of the phenyl, pyridyl, and naphthyl optionally is substituted with one or more moieties from the group consisting of F, Cl, Br, -CN, -OH, -SH, C₁₋₆ alkyl, C₁₋₆ alkoxy, and C₁₋₆ alkylthio; and

G is selected from the group consisting of

- 25 a) C₁₋₄ alkyl, b) C₅₋₈ alkyl, c) C₂₋₈ alkenyl, d) C₂₋₈ alkynyl, e) C₁₋₈ alkoxy,
f) C₁₋₈ alkylthio, g) C₁₋₈ acyl, h) saturated, unsaturated, or aromatic C₅₋₁₀ carbocycle, i) saturated, unsaturated, or aromatic 5-10 membered

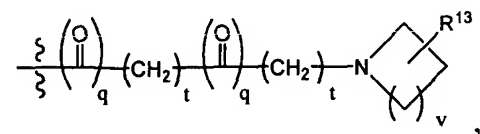
heterocycle containing one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur,

j)

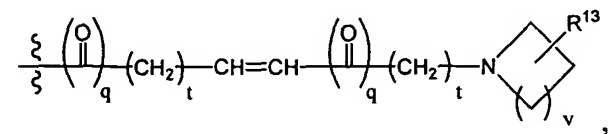


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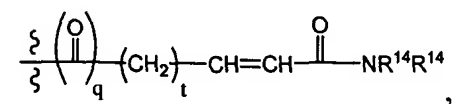
k)



l)

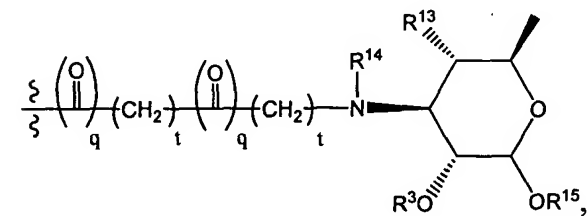


m)

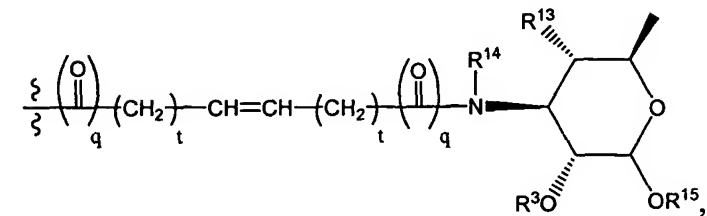


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n)



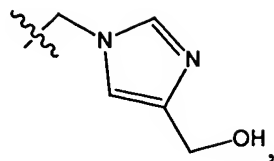
o)



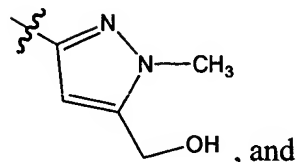
15

p)

x)

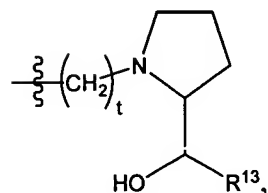


y)



5

z)



wherein

i) a) is substituted with, and

ii) any of b) – i) optionally is substituted with one or more moieties selected from the group consisting of:

carbonyl; formyl; F; Cl; Br; I; CN; NO₂; OR³; -S(O)_rR⁵;
 -S(O)_rN=R², -C(O)R²; -C(O)OR³; -OC(O)R²; -C(O)NR²R²;
 -OC(O)NR²R²; -C(=NR¹²)R²; -C(R²)(R²)OR³;
 -C(R²)(R²)OC(O)R²; -C(R²)(OR³)(CH₂)_rNR²R²; -NR²R²;
 -NR²OR³; -NR²C(O)R²; -NR²C(O)OR³; -NR²C(O)NR²R²;
 -NR²S(O)_rR⁵; -C(OR⁶)(OR⁶)R²; -C(R²)(R³)NR²R²;
 -C(R²)(R³)NR²R¹²; =NR¹²; -C(S)NR²R²; -NR²C(S)R²;
 -OC(S)NR²R²; -NR²C(S)OR³; -NR²C(S)NR²R²; -SC(O)R²;
 C₂₋₅ alkenyl; C₂₋₅ alkynyl; C₁₋₈ alkoxy; C₁₋₈ alkylthio; C₁₋₈ acyl;
 saturated, unsaturated, or aromatic C₅₋₁₀ carbocycle, optionally
 substituted with one or more R¹³ groups; and saturated,

unsaturated, or aromatic 5-10 membered heterocycle containing one or more heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur, and optionally substituted with one or more R^{13} groups;

5 t, at each occurrence, independently is 0, 1, 2, or 3;

v is 0, 1, 2, 3, 4, 5, or 6;

K' is O, NR^2 , or $S(O)_r$;

R^{55} , at each occurrence, independently is hydrogen, $-CH_2OH$, or C_{1-4} alkyl;

alternatively, two R^{55} groups taken together are a carbonyl group;

10 R^{14} is selected from the group consisting of:

a) hydrogen, b) C_{1-6} -alkyl, c) C_{2-6} alkenyl, d) C_{2-6} alkynyl, e) $-C(O)-R^3$,
f) $-C(O)-C_{1-6}$ alkyl- R^3 , g) $-C(O)-C_{2-6}$ alkenyl- R^3 , h) $-C(O)-C_{2-6}$ alkynyl- R^3 ,
i) $-C_{1-6}$ alkyl-J- R^3 , j) $-C_{2-6}$ alkenyl-J- R^3 ; and k) $-C_{2-6}$ alkynyl-J- R^3 ;

wherein

15 (i) any of b) – d) optionally is substituted with one or more substituents selected from the group consisting of:

F, Cl, Br, I, aryl, substituted aryl, heteroaryl, substituted heteroaryl,
 $-OR^3$, $-O-C_{1-6}$ alkyl- R^2 , $-O-C_{2-6}$ alkenyl- R^2 , $-O-C_{2-6}$ alkynyl- R^2 ,
and $-NR^2R^2$; and

20 (ii) J is selected from the group consisting of:

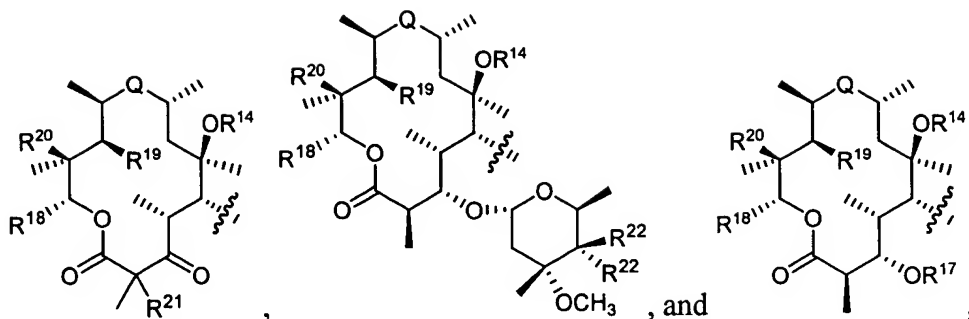
$-OC(O)-$, $-OC(O)O-$, $-OC(O)NR^2-$, $-C(O)NR^2-$, $-NR^2C(O)-$,
 $-NR^2C(O)O-$, $-NR^2C(O)NR^2-$, $-NR^2C(NH)NR^2-$, and $S(O)_r$; and

R^{15} is selected from the group consisting of:

hydrogen; C_{1-10} alkyl, optionally substituted with one or more R^{13} groups;

25 C_{1-6} acyl, optionally substituted with one or more R^{13} groups; aryl; substituted aryl; heteroaryl; substituted heteroaryl; arylalkyl; substituted arylalkyl; and a macrolide;

wherein the macrolide is selected from the group consisting of:



and pharmaceutically acceptable salts, esters and prodrugs thereof, wherein

R^{17} is selected from the group consisting of:

hydrogen, hydroxy protecting group, R^3 , and $-V-W-R^{13}$,

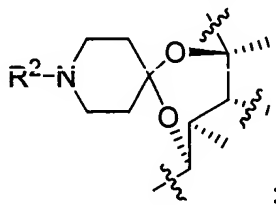
5

wherein

V is $-C(O)$, $-C(O)O-$, $-C(O)NR^2-$, or absent, and

W is C_{1-6} alkyl, or absent;

alternatively R^{17} and R^{14} , taken together with the atoms to which they are bonded, form:



10

Q is selected from the group consisting of:

$-NR^2CH_2-$, $-CH_2-NR^2-$, $-C(O)-$, $-C(=NR^2)-$, $-C(=NOR^3)-$, $-C(=N-NR^2R^2)-$,
 $-CH(OR^3)-$, and $-CH(NR^2R^2)-$;

R^{18} is selected from the group consisting of:

i) C_{1-6} alkyl, ii) C_{2-6} alkenyl, and iii) C_{2-6} alkynyl;

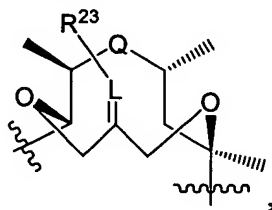
15

wherein any of i) – iii) optionally is substituted with one or more moieties
selected from the group consisting of $-OR^3$, aryl, substituted aryl,
heteroaryl, and substituted heteroaryl;

R^{19} is selected from the group consisting of:

a) $-OR^{17}$, b) C_{1-6} alkyl, c) C_{2-6} alkenyl, d) C_{2-6} alkynyl, e) $-NR^2R^2$, f) $-C(O)R^3$,
20 g) $-C(O)-C_{1-6}$ alkyl- R^{13} , h) $-C(O)-C_{2-6}$ alkenyl- R^{13} , and i) $-C(O)-C_{2-6}$ alkynyl- R^{13} ,
wherein any of b) - d) optionally is substituted with one or more R^{13}
groups;

alternatively, R^{14} and R^{19} , taken together with the atoms to which they are bonded, form:



wherein

L is CH or N , and

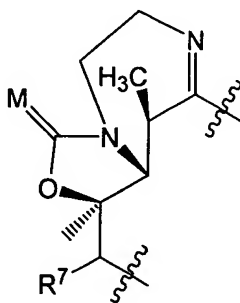
5 R^{23} is $-OR^3$, or R^3 ;

R^{20} is $-OR^{17}$;

alternatively, R^{19} and R^{20} , taken together with the atoms to which they are bonded, form a 5-membered ring by attachment to each other through a linker selected from the group consisting of:

10 $-OC(R^2)(R^2)O-$, $-OC(O)O-$, $-OC(O)NR^2-$, $-NR^2C(O)O-$, $-OC(O)NOR^3-$,
 $-N(OR^3)C(O)O-$, $-OC(O)N-NR^2R^2-$, $-N(NR^2R^2)C(O)O-$, $-OC(O)CHR^2-$, $-CHR^2C(O)O-$,
 $-OC(S)O-$, $-OC(S)NR^2-$, $-NR^2C(S)O-$, $-OC(S)NOR^3-$, $-N(OR^3)C(S)O-$,
 $-OC(S)N-NR^2R^2-$, $-N(NR^2R^2)C(S)O-$, $-OC(S)CHR^2-$, and $-CHR^2C(S)O-$;

alternatively, Q , R^{19} , and R^{20} , taken together with the atoms to which they are bonded,
 15 form:



wherein

M is O or NR^2 ;

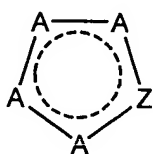
R^{21} is selected from the group consisting of:

20 hydrogen, F , Cl , Br , I , and C_{1-6} alkyl;

R^{22} , at each occurrence, independently is selected from the group consisting of:

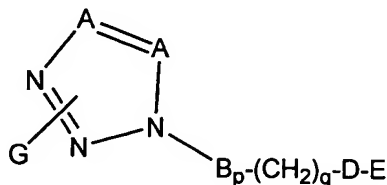
hydrogen, $-OR^3$, $-O$ -hydroxy protecting group, $-O-C_{1-6}$ alkyl- $J-R^{13}$,
 $-O-C_{2-6}$ alkenyl- $J-R^{13}$, $-O-C_{1-6}$ alkynyl- $J-R^{13}$, and $-NR^2R^2$;
 alternatively, two R^{22} groups taken together are $=O$, $=N-OR^3$, or $=N-NR^2R^2$; and
 R^2 , R^3 , R^{13} , R^{14} , and J are as described hereinabove.

5 Examples of:



include, but are not limited to, thiophene, furan, 4-oxo-2-imidazolyl, 2-imidazolyl, 4-imidazolyl,
 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, 1-pyrazolyl, 3-pyrazolyl, 4-pyrazolyl, 5-pyrazolyl, 2-
 oxazolyl, 4-oxazolyl, 4-oxo-2-oxazolyl, 5-oxazolyl, 4,5,-dihydrooxazole, 1,2,3-oxadiazole, 1,2,4-
 10 oxadiazole, 1,2,5-oxadiazole, 1,3,4-oxadiazole, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 3-
 isothiazole, 4-isothiazole, 5-isothiazole, 2-furanyl, 3-furanyl, 2-thienyl, 3-thienyl, 1-pyrrolyl, 2-
 pyrrolyl, 3-pyrrolyl, 1,2,4-oxadiazol-3-yl, 1,2,4-oxadiazol-5-yl, 5-oxo-1,2,4-oxadiazol-3-yl,
 1,2,4-thiadiazol-3-yl, 1,2,4-thiadiazol-5-yl, 3-oxo-1,2,4-thiadiazol-5-yl, 1,3,4-thiadiazol-5-yl, 2-
 oxo-1,3,4-thiadiazol-5-yl, 1,2,3-triazol-1-yl, 1,2,3-triazol-4-yl, 1,2,3-triazol-5-yl, 1,2,4-triazol-1-
 15 yl, 1,2,4-triazol-3-yl, 1,2,4-triazol-5-yl, 1-tetrazol-5-yl, 2-tetrazol-5-yl, 3-isothiazolyl, 4-
 isothiazolyl and 5-isothiazolyl, 4-oxo-2-thiazolinyl, or 5-methyl-1,3,4-thiadiazol-2-yl,
 thiazolidine-2,4-dione, oxazolidine-2,4-dione, imidazolidine-2,4-dione, oxazolidin-2-one,
 thiazolidin-2-one, 3H-oxazol-2-one, 1,3-dihydro-imidazol-2-one, 1,3-dihydro-imidazole-2-
 thione, 2-thioxo-imidazolidin-4-one, and 4-thioxo-imidazolidin-2-one.

20 In certain embodiments, the invention provides compounds having the formula:

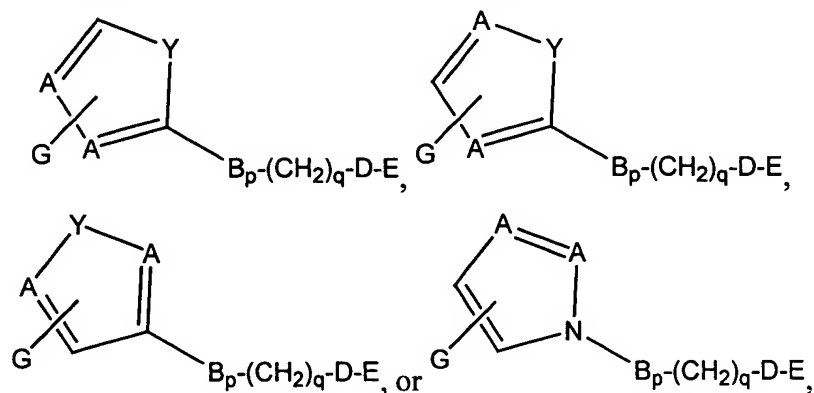


wherein

A , at each occurrence, independently is carbon or nitrogen, provided at
 least one A is carbon, and

25 p , q , B , D , E , and G are as defined hereinabove.

Other embodiments of the invention include compounds having the formula:



wherein

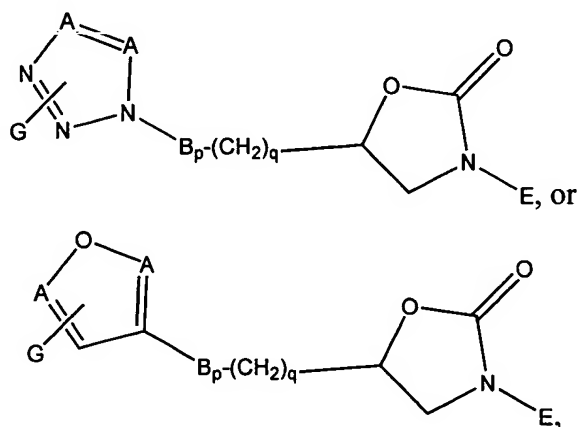
5

Y is oxygen or sulfur,

A, at each occurrence, independently is carbon or nitrogen, and

p, q, B, D, E, and G are as defined hereinabove.

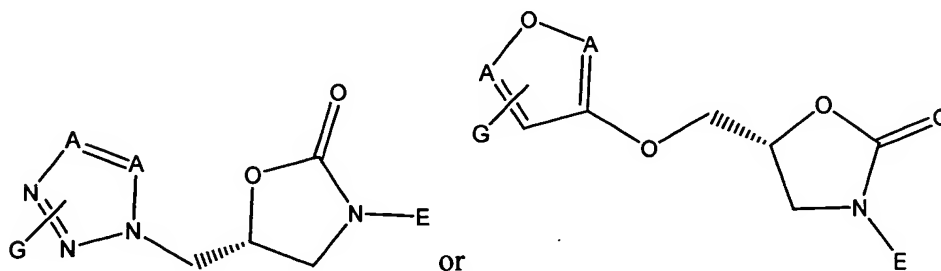
In other embodiments, the invention provides compounds having the formula:



10

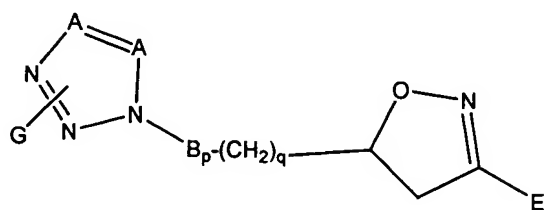
wherein p, q, A, B, E, and G are as defined hereinabove.

Features of these embodiments include compounds having the formula:

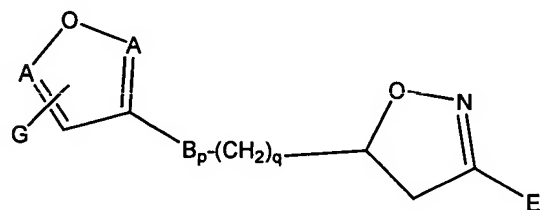


wherein A, E, and G are as defined hereinabove.

In some embodiments, the invention provides compounds having the formula:

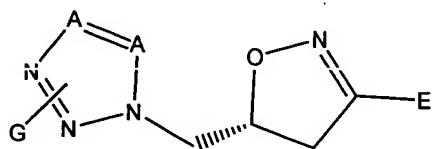


or



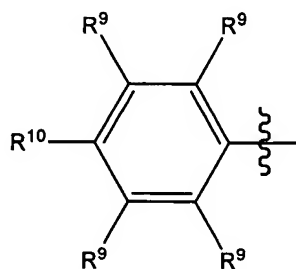
5 wherein p, q, A, E, and G are as defined hereinabove.

Features of these embodiments include compounds having the formula:



wherein A, E, and G are as defined hereinabove.

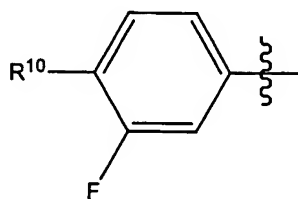
In certain embodiments, E has the formula:



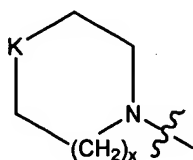
10

wherein R^9 and R^{10} , at each occurrence, are as defined hereinabove.

Features of this embodiment include compounds wherein E has the formula:



Other features of this embodiment include compounds wherein R¹⁰ has the formula:



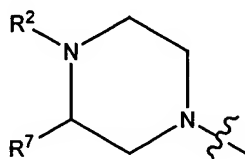
wherein K is selected from the group consisting of O, NR^2 , and S(O)_r , and

x is 0, 1, 2, or 3.

5 In certain features of this embodiment, K is oxygen, and in other features, t is 1.

Still other features of this embodiment include compounds wherein R¹⁰ is -C(O)CH₃.

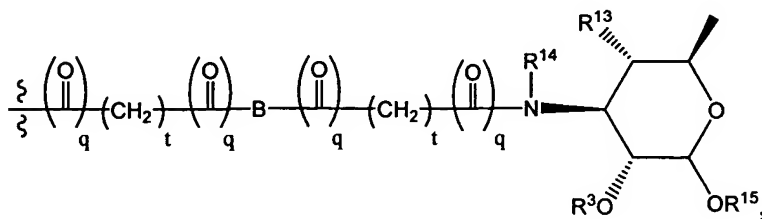
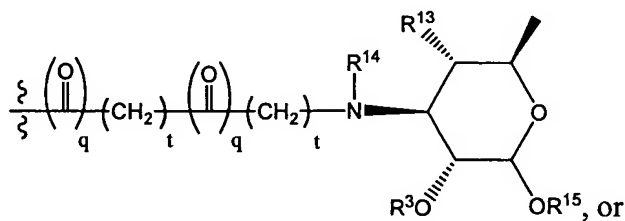
Yet another feature of this embodiment includes compounds wherein R¹⁰ has the formula:



wherein R² and R⁷ are as defined hereinabove.

10 Certain other features of this embodiment include compounds wherein R^2 is $-C(O)-CH_2-OH$. In other features, R^7 is hydrogen.

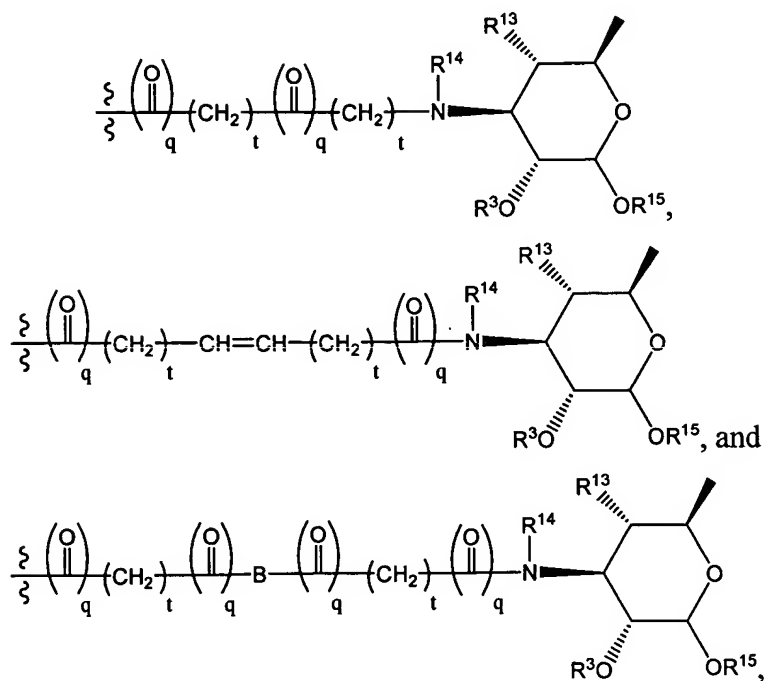
In other embodiments according to the invention, in the foregoing compounds, G has the formula:



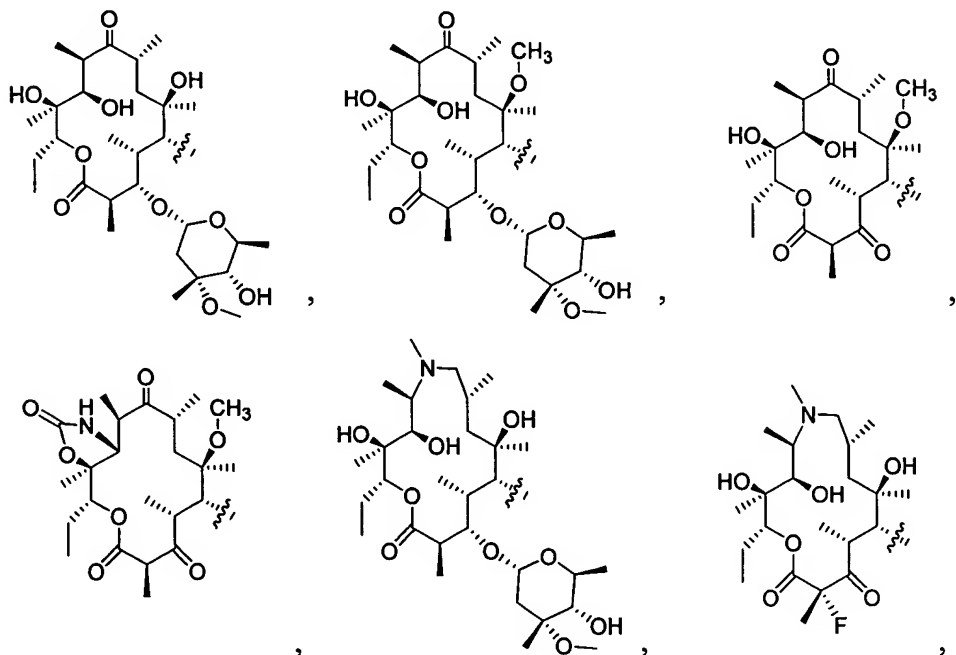
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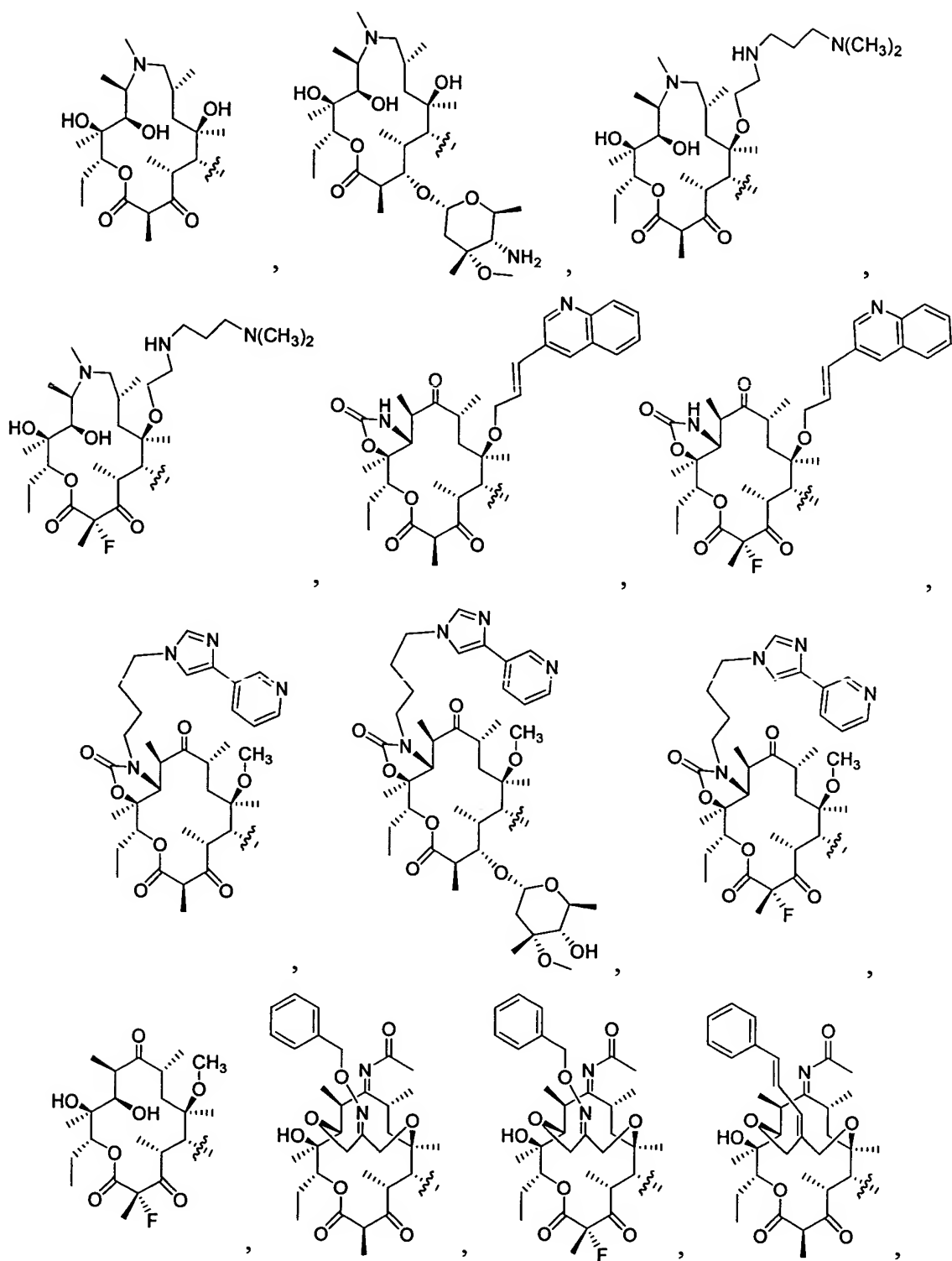
wherein R¹⁵ is a macrolide.

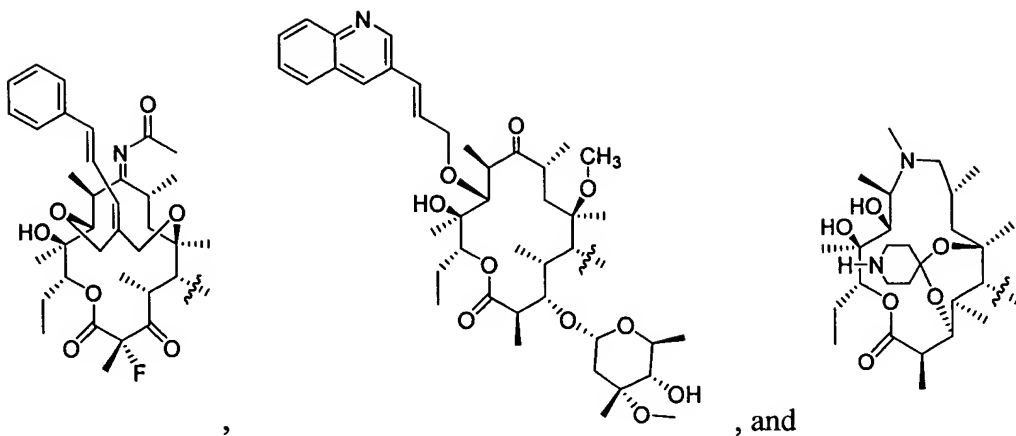
consisting of:



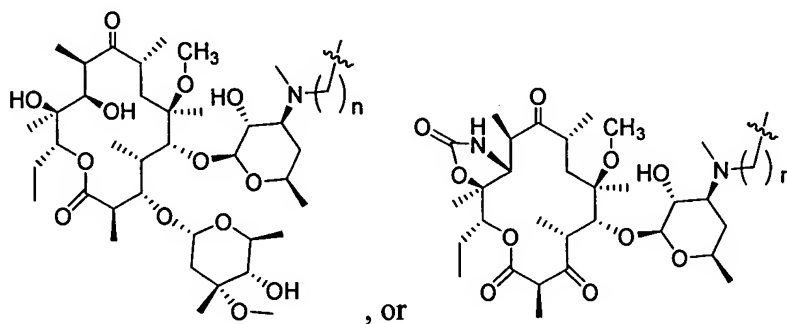
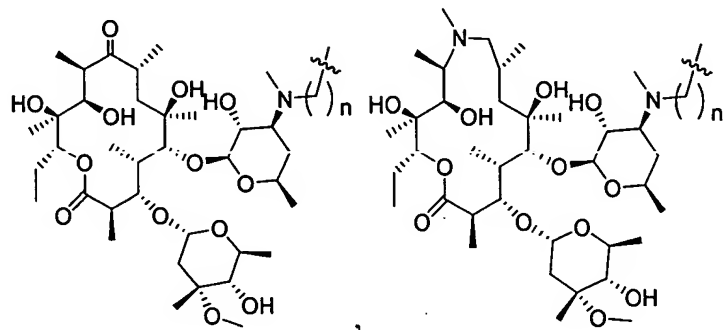
and R^{15} is selected from the group consisting of:





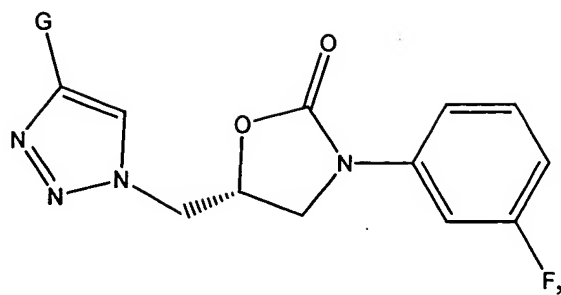


In another embodiments according to the invention, in the foregoing compounds, G has the formula:

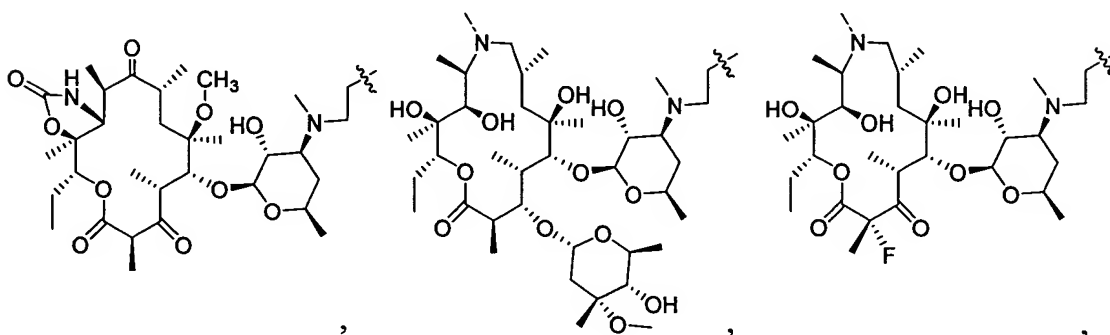
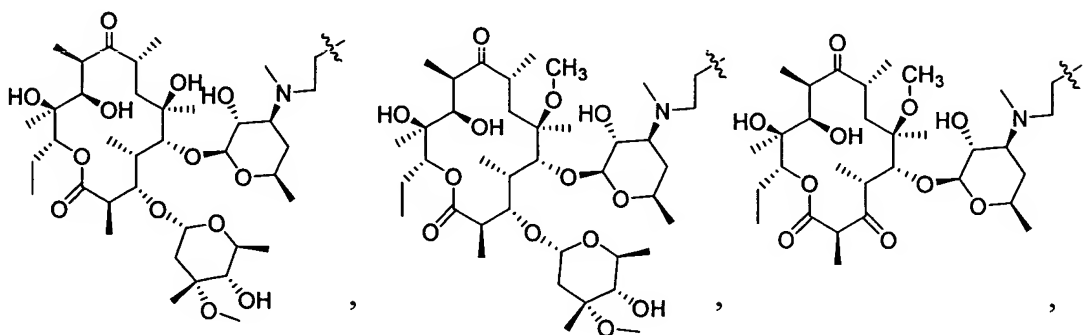


wherein n is 1, 2, 3, or 4.

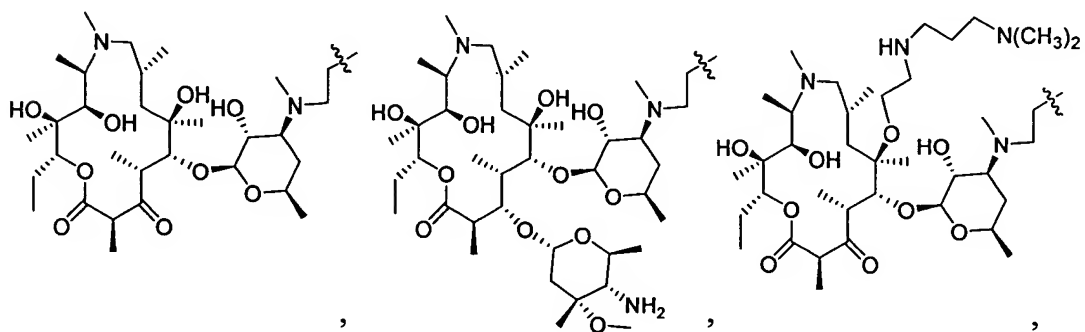
In still other embodiments, the invention provides compounds having the formula:

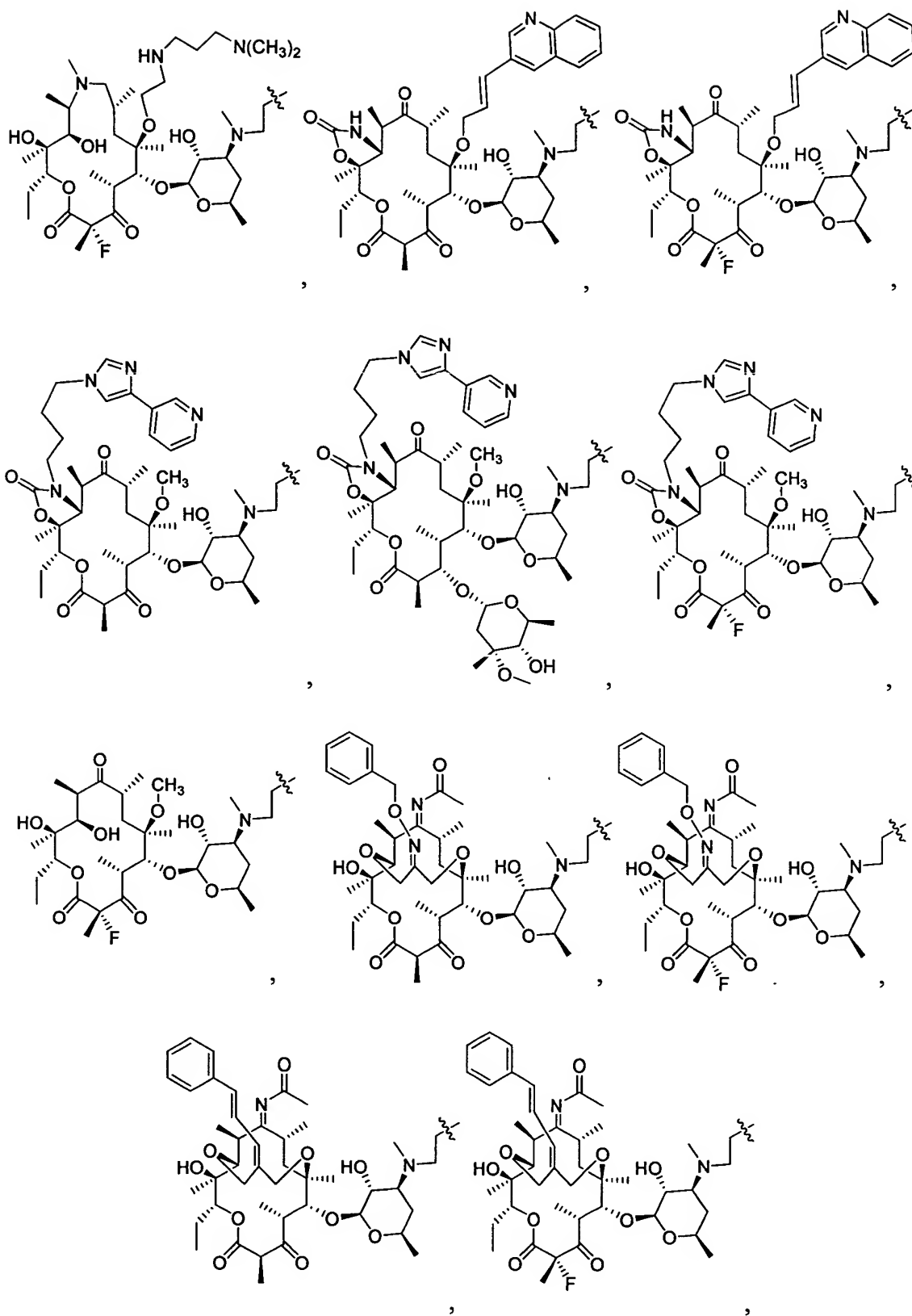


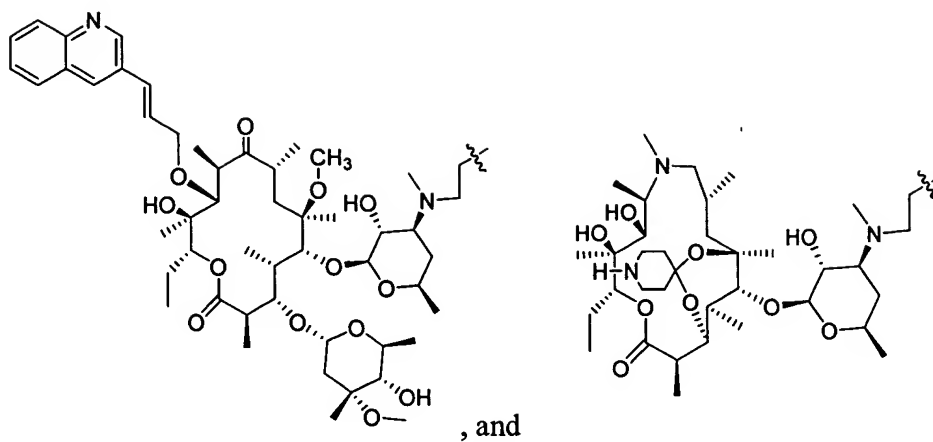
wherein G is as described hereinabove. Features of this embodiment include compounds wherein G is selected from the group consisting of:



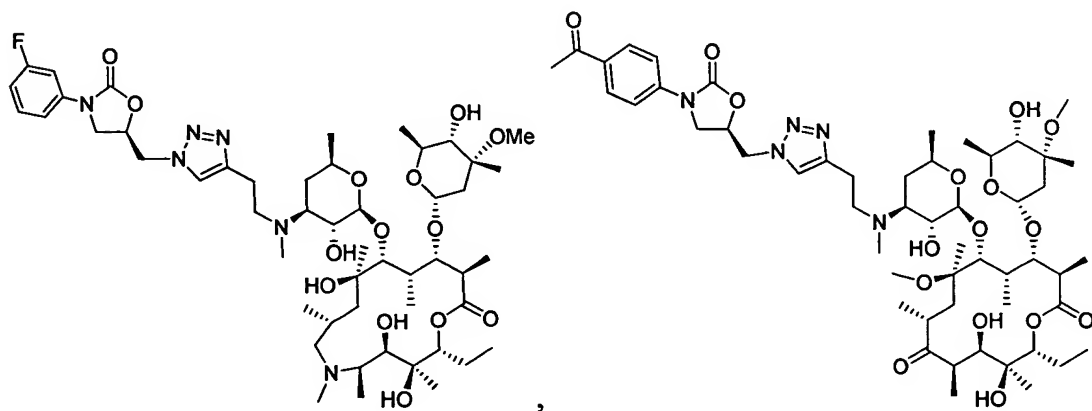
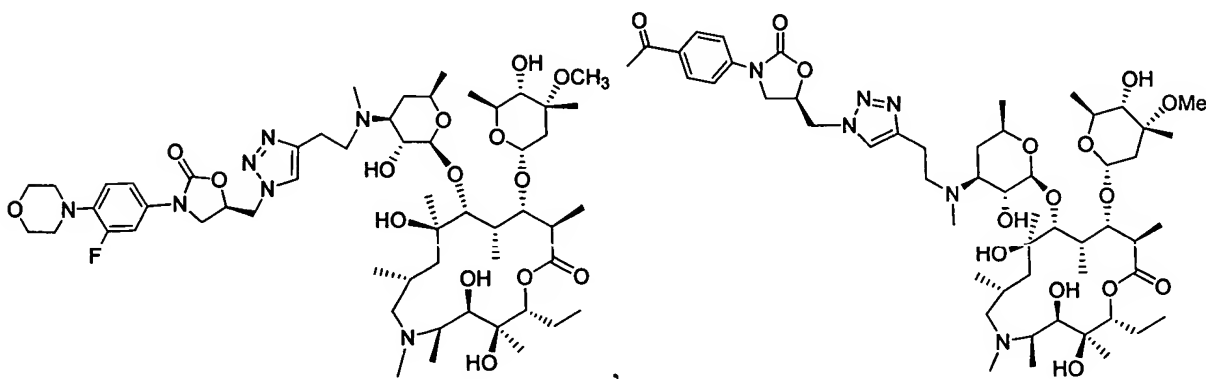
5

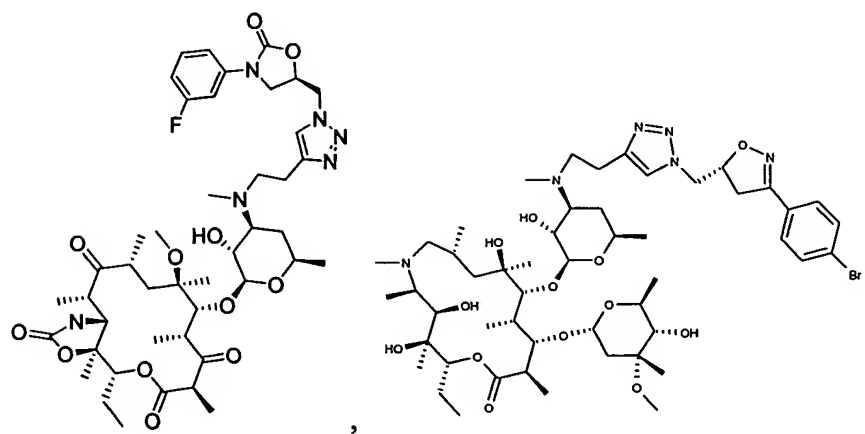
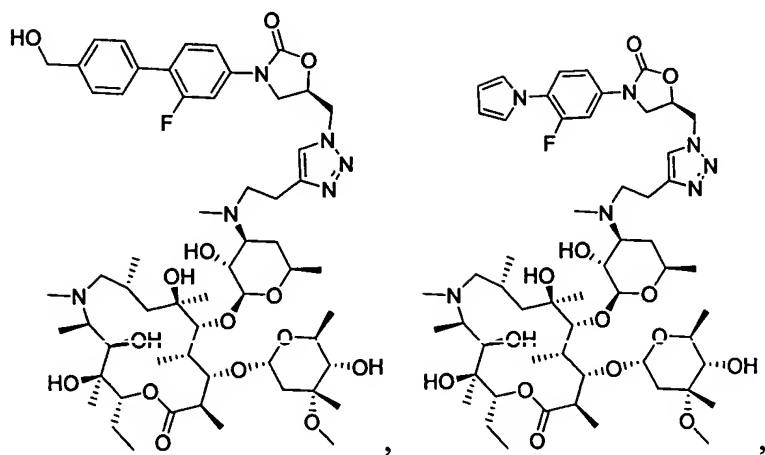
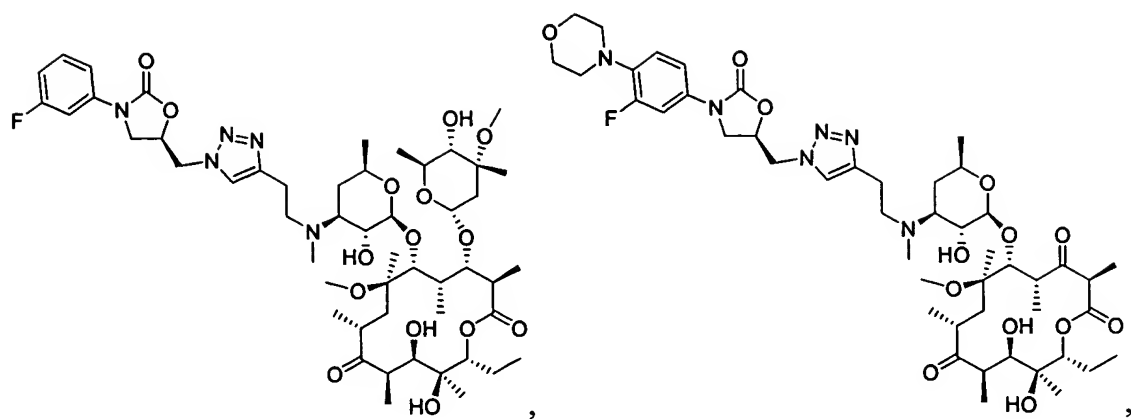


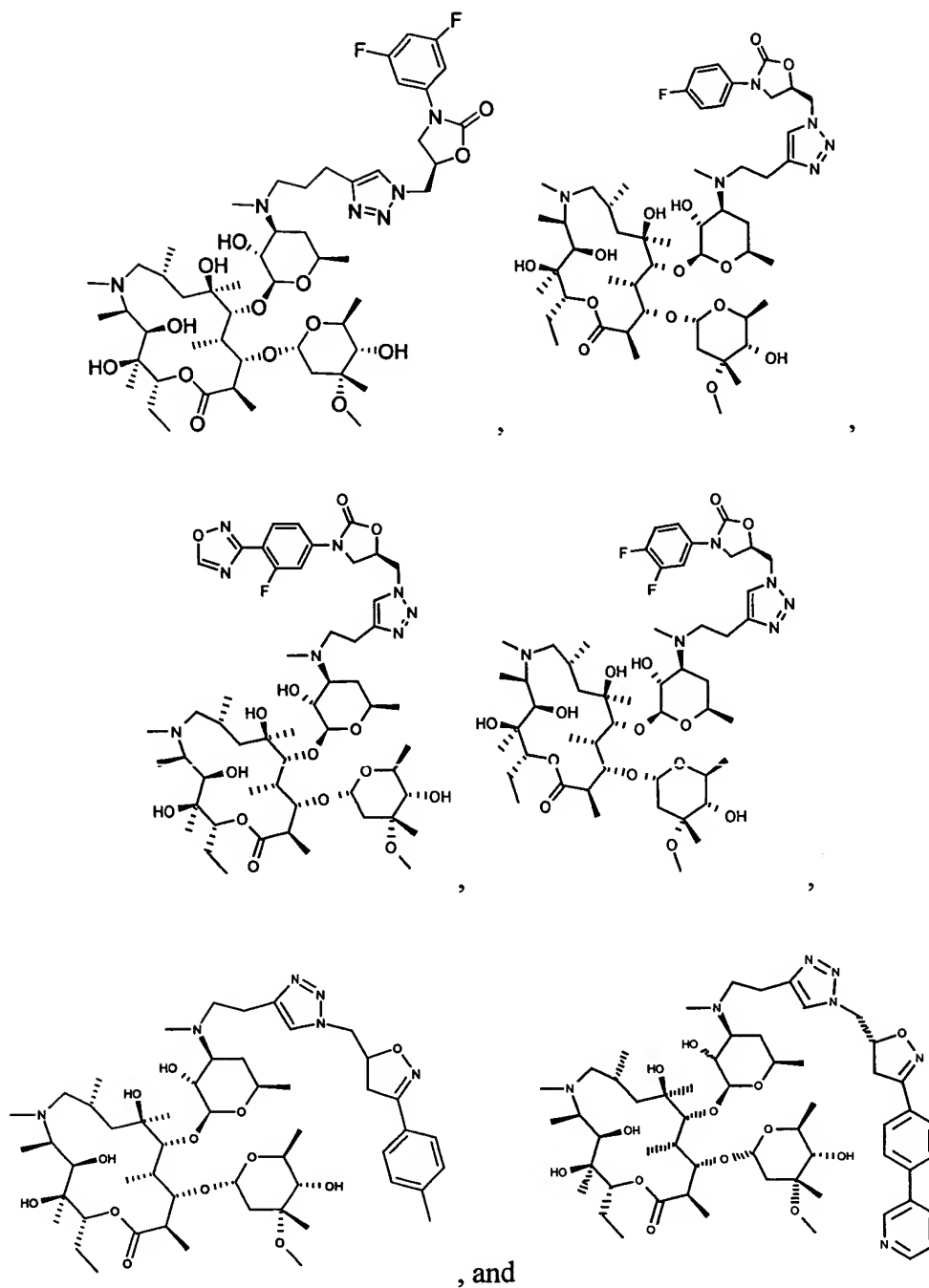




Other embodiments of the invention include compounds having the formula selected from:







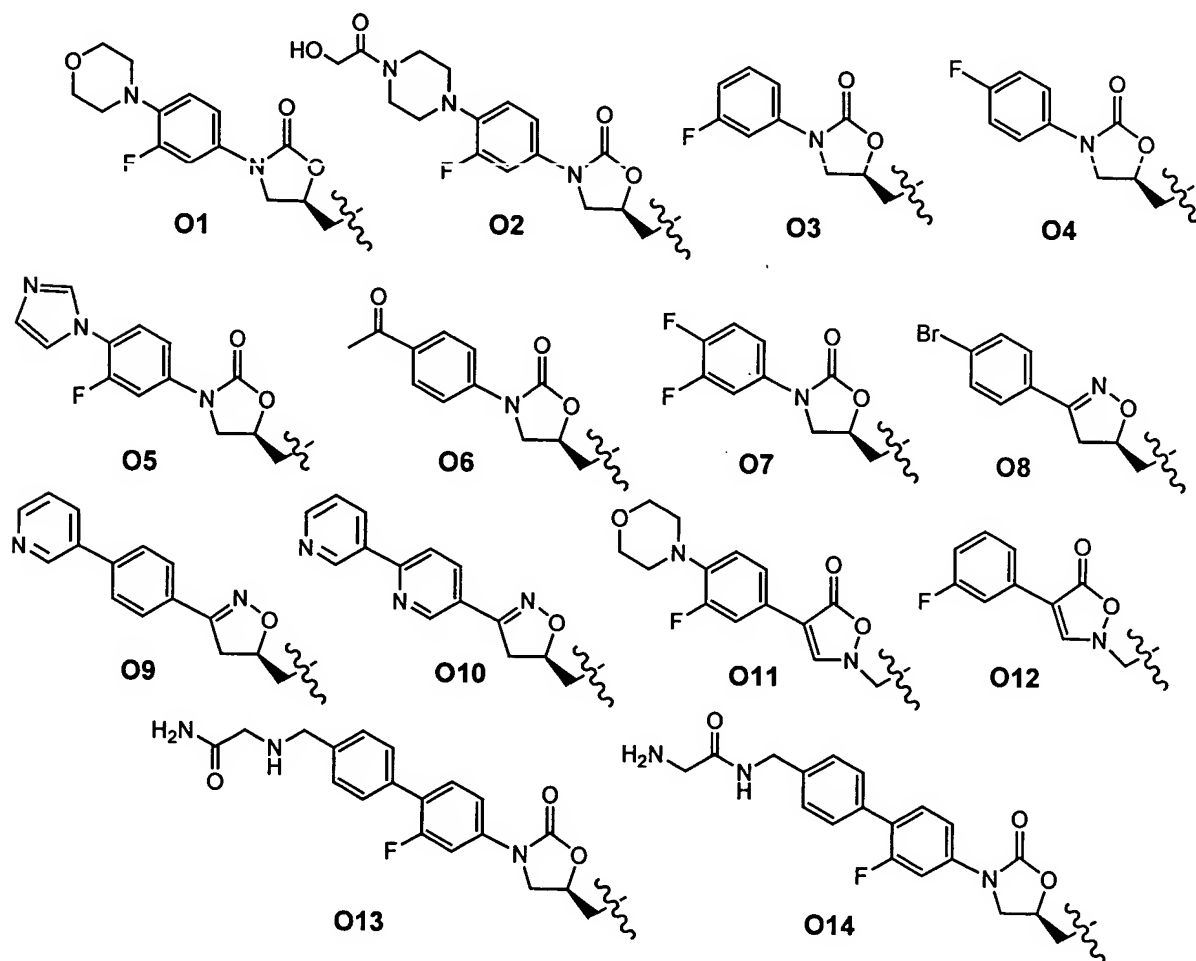
or a pharmaceutically acceptable salt, ester, or prodrug thereof.

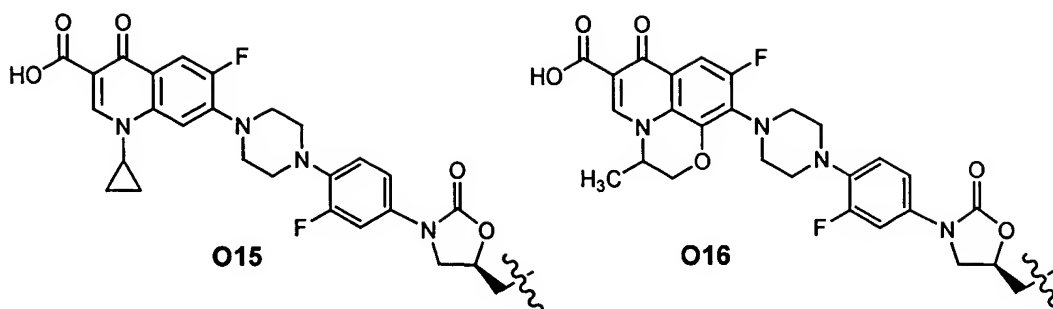
- 5 In another aspect, the invention provides a pharmaceutical composition comprising a therapeutically effective amount of one or more of the foregoing compounds and a pharmaceutically acceptable carrier. In yet another aspect, the invention provides a method for treating a microbial infection, a fungal infection, a viral infection, a parasitic disease, a proliferative disease, an inflammatory disease, or a gastrointestinal motility disorder in a

mammal by administering effective amounts of the compounds of the invention or pharmaceutical compositions of the invention, for example, via oral, parenteral or topical routes. In still another aspect, the invention provides methods for synthesizing any one of the foregoing compounds. In another aspect, the invention provides a medical device, for example, a medical stent, which contains or is coated with one or more of the foregoing compounds.

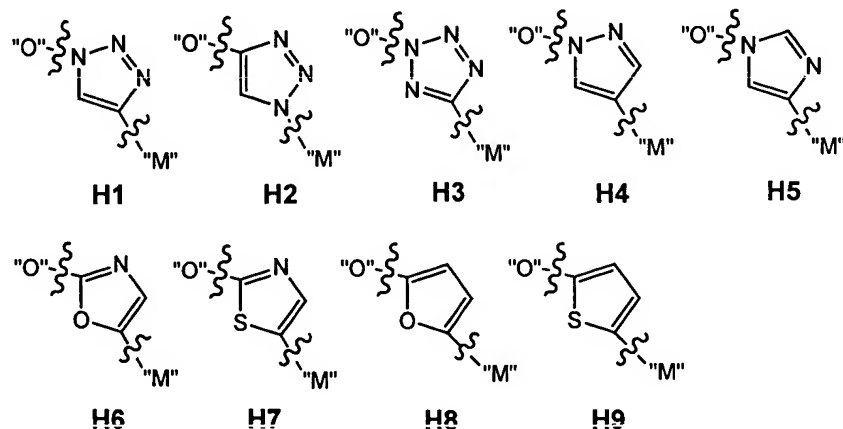
In another embodiment, the invention further provides a family of hybrid antibiotics comprising a heterocyclic side-chain linked via a heterocyclic linker to at least a portion of a macrolide-based antibiotic. Exemplary heterocyclic side-chains, heterocyclic linkers, and macrolides useful in the synthesis of the hybrid antibiotics include, but are not limited to, the chemical moieties shown below:

Heterocyclic Side-chains





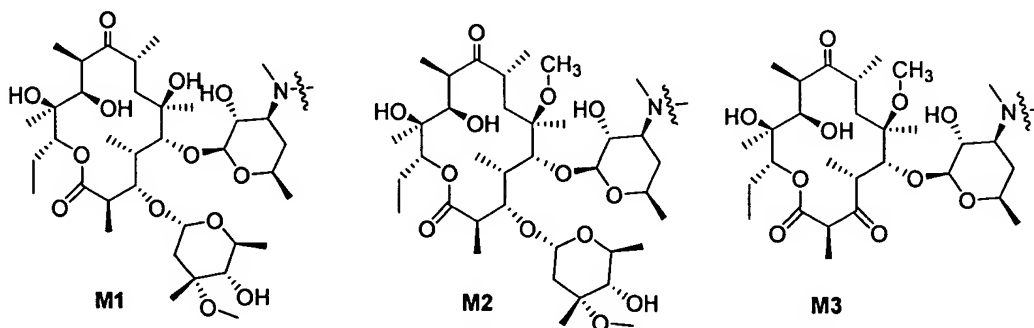
Heterocyclic Linkers

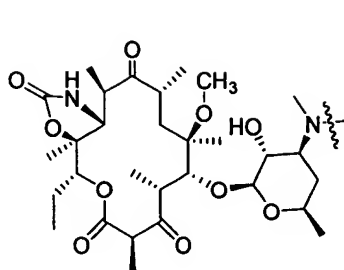


5 For the above heterocyclic linkers, it should be understood that “O” and “M” are included to depict the orientation of the heterocyclic linker with respect to the other structures that define the compounds of the invention. More specifically, “O” denotes the portion of the compound that includes the heterocyclic side-chain moiety, and “M” denotes the portion of the compound that includes the macrolide moiety.

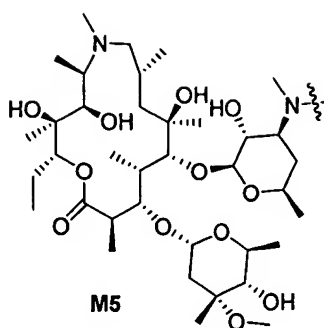
10

Macrolides

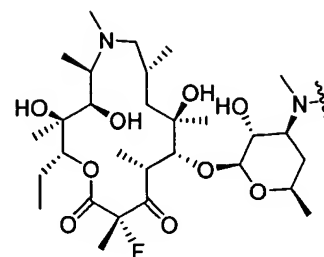




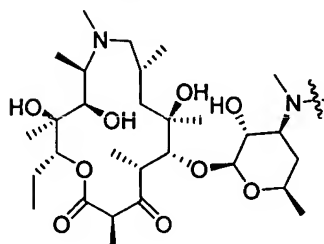
M4



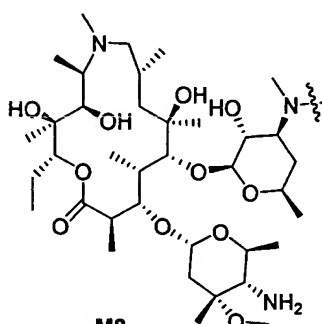
M5



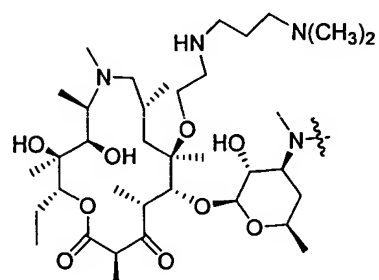
M6



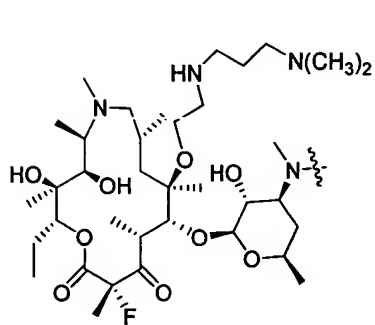
M7



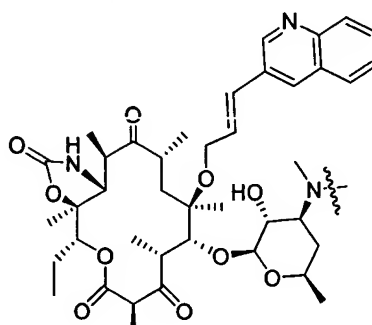
M8



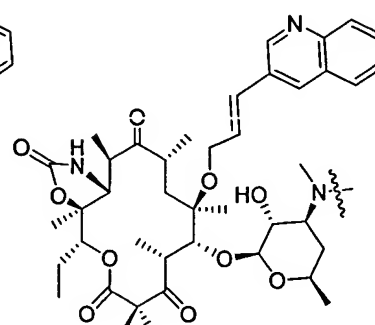
M9



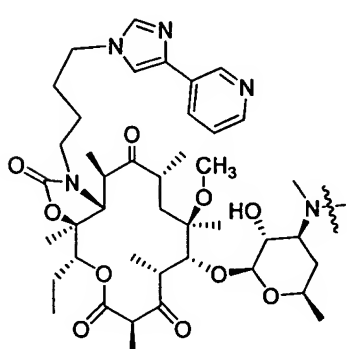
M10



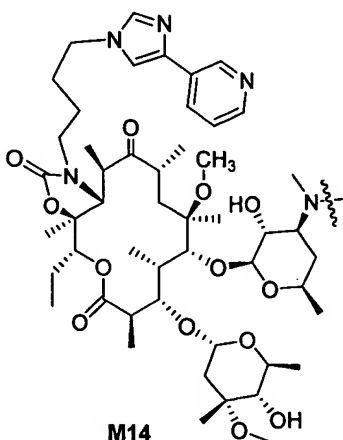
M11



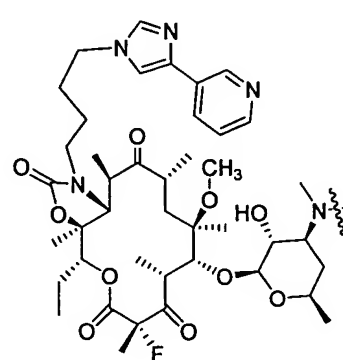
M12



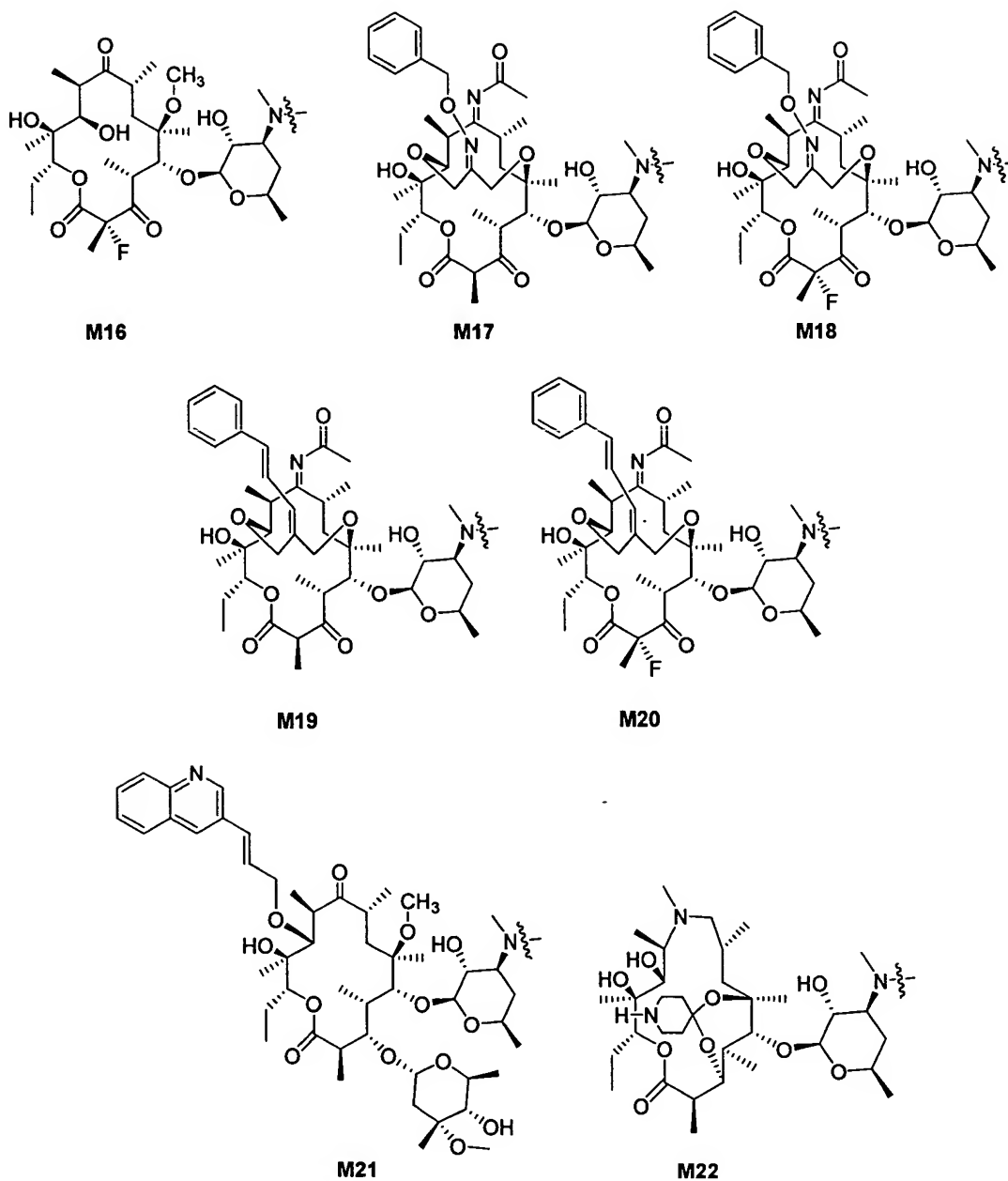
M13



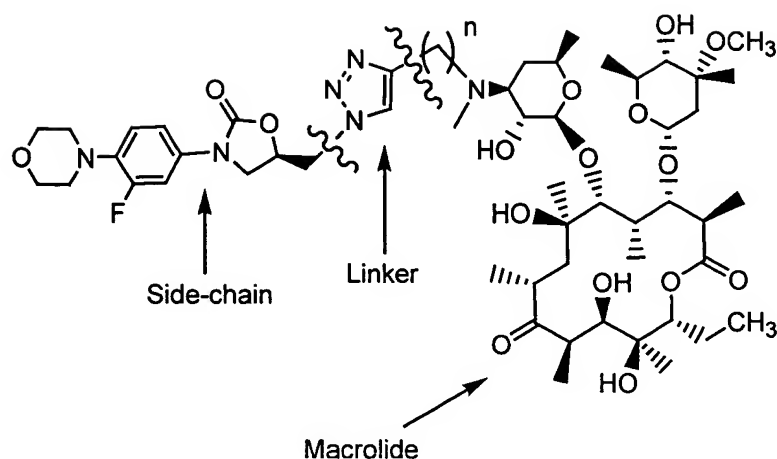
M14



M15



An exemplary scheme showing the linkage of a heterocyclic side-chain to a macrolide via a heterocyclic linker is shown below, where n can be 1, 2, 3, or 4:



The various heterocyclic side-chains may be linked via the heterocyclic linkers to the macrolides using conventional chemistries known in the art, such as those discussed below. By using the various combinations of chemical moieties provided, the skilled artisan may synthesize one or more of the exemplary compounds listed in Table 1. For each set of examples, the four lower case letter designations denote three compounds where $n = 1, 2, 3,$ or 4 . For example, as a guide to the following table, compound **E1a** is the $n = 1$ variant of the structure shown on the same row of the table. Compound **E1b** is the $n = 2$ derivative, compound **E1c** is the $n = 3$ derivative, and **E1d** is the $n = 4$ derivative.

TABLE 1

Example	O Group	H Group	M Group
E1a-d	O1	H1	M1
E2a-d	O1	H2	M1
E3a-d	O1	H3	M1
E4a-d	O1	H4	M1
E5a-d	O1	H5	M1
E6a-d	O1	H6	M1
E7a-d	O1	H7	M1
E8a-d	O1	H8	M1
E9a-d	O1	H9	M1
E10a-d	O2	H1	M1
E11a-d	O2	H2	M1
E12a-d	O2	H3	M1
E13a-d	O2	H4	M1
E14a-d	O2	H5	M1
E15a-d	O2	H6	M1
E16a-d	O2	H7	M1
E17a-d	O2	H8	M1

Example	O Group	H Group	M Group
E18a-d	O2	H9	M1
E19a-d	O3	H1	M1
E20a-d	O3	H2	M1
E21a-d	O3	H3	M1
E22a-d	O3	H4	M1
E23a-d	O3	H5	M1
E24a-d	O3	H6	M1
E25a-d	O3	H7	M1
E26a-d	O3	H8	M1
E27a-d	O3	H9	M1
E28a-d	O4	H1	M1
E29a-d	O4	H2	M1
E30a-d	O4	H3	M1
E31a-d	O4	H4	M1
E32a-d	O4	H5	M1
E33a-d	O4	H6	M1
E34a-d	O4	H7	M1
E35a-d	O4	H8	M1
E36a-d	O4	H9	M1
E37a-d	O5	H1	M1
E38a-d	O5	H2	M1
E39a-d	O5	H3	M1
E40a-d	O5	H4	M1
E41a-d	O5	H5	M1
E42a-d	O5	H6	M1
E43a-d	O5	H7	M1
E44a-d	O5	H8	M1
E45a-d	O5	H9	M1
E46a-d	O6	H1	M1
E47a-d	O6	H2	M1
E48a-d	O6	H3	M1
E49a-d	O6	H4	M1
E50a-d	O6	H5	M1
E51a-d	O6	H6	M1
E52a-d	O6	H7	M1
E53a-d	O6	H8	M1
E54a-d	O6	H9	M1
E55a-d	O7	H1	M1
E56a-d	O7	H2	M1
E57a-d	O7	H3	M1
E58a-d	O7	H4	M1
E59a-d	O7	H5	M1
E60a-d	O7	H6	M1
E61a-d	O7	H7	M1

Example	O Group	H Group	M Group
E62a-d	O7	H8	M1
E63a-d	O7	H9	M1
E64a-d	O8	H1	M1
E65a-d	O8	H2	M1
E66a-d	O8	H3	M1
E67a-d	O8	H4	M1
E68a-d	O8	H5	M1
E69a-d	O8	H6	M1
E70a-d	O8	H7	M1
E71a-d	O8	H8	M1
E72a-d	O8	H9	M1
E73a-d	O9	H1	M1
E74a-d	O9	H2	M1
E75a-d	O9	H3	M1
E76a-d	O9	H4	M1
E77a-d	O9	H5	M1
E78a-d	O9	H6	M1
E79a-d	O9	H7	M1
E80a-d	O9	H8	M1
E81a-d	O9	H9	M1
E82a-d	O10	H1	M1
E83a-d	O10	H2	M1
E84a-d	O10	H3	M1
E85a-d	O10	H4	M1
E86a-d	O10	H5	M1
E87a-d	O10	H6	M1
E88a-d	O10	H7	M1
E89a-d	O10	H8	M1
E90a-d	O10	H9	M1
E91a-d	O11	H1	M1
E92a-d	O11	H2	M1
E93a-d	O11	H3	M1
E94a-d	O11	H4	M1
E95a-d	O11	H5	M1
E96a-d	O11	H6	M1
E97a-d	O11	H7	M1
E98a-d	O11	H8	M1
E99a-d	O11	H9	M1
E100a-d	O12	H1	M1
E101a-d	O12	H2	M1
E102a-d	O12	H3	M1
E103a-d	O12	H4	M1
E104a-d	O12	H5	M1
E105a-d	O12	H6	M1

Example	O Group	H Group	M Group
E106a-d	O12	H7	M1
E107a-d	O12	H8	M1
E108a-d	O12	H9	M1
E109a-d	O13	H1	M1
E110a-d	O13	H2	M1
E111a-d	O13	H3	M1
E112a-d	O13	H4	M1
E113a-d	O13	H5	M1
E114a-d	O13	H6	M1
E115a-d	O13	H7	M1
E116a-d	O13	H8	M1
E117a-d	O13	H9	M1
E118a-d	O14	H1	M1
E119a-d	O14	H2	M1
E120a-d	O14	H3	M1
E121a-d	O14	H4	M1
E122a-d	O14	H5	M1
E123a-d	O14	H6	M1
E124a-d	O14	H7	M1
E125a-d	O14	H8	M1
E126a-d	O14	H9	M1
E127a-d	O15	H1	M1
E128a-d	O15	H2	M1
E129a-d	O15	H3	M1
E130a-d	O15	H4	M1
E131a-d	O15	H5	M1
E132a-d	O15	H6	M1
E133a-d	O15	H7	M1
E134a-d	O15	H8	M1
E135a-d	O15	H9	M1
E136a-d	O16	H1	M1
E137a-d	O16	H2	M1
E138a-d	O16	H3	M1
E139a-d	O16	H4	M1
E140a-d	O16	H5	M1
E141a-d	O16	H6	M1
E142a-d	O16	H7	M1
E143a-d	O16	H8	M1
E144a-d	O16	H9	M1
E145a-d	O1	H1	M2
E146a-d	O1	H2	M2
E147a-d	O1	H3	M2
E148a-d	O1	H4	M2
E149a-d	O1	H5	M2

Example	O Group	H Group	M Group
E150a-d	O1	H6	M2
E151a-d	O1	H7	M2
E152a-d	O1	H8	M2
E153a-d	O1	H9	M2
E154a-d	O2	H1	M2
E155a-d	O2	H2	M2
E156a-d	O2	H3	M2
E157a-d	O2	H4	M2
E158a-d	O2	H5	M2
E159a-d	O2	H6	M2
E160a-d	O2	H7	M2
E161a-d	O2	H8	M2
E162a-d	O2	H9	M2
E163a-d	O3	H1	M2
E164a-d	O3	H2	M2
E165a-d	O3	H3	M2
E166a-d	O3	H4	M2
E167a-d	O3	H5	M2
E168a-d	O3	H6	M2
E169a-d	O3	H7	M2
E170a-d	O3	H8	M2
E171a-d	O3	H9	M2
E172a-d	O4	H1	M2
E173a-d	O4	H2	M2
E174a-d	O4	H3	M2
E175a-d	O4	H4	M2
E176a-d	O4	H5	M2
E177a-d	O4	H6	M2
E178a-d	O4	H7	M2
E179a-d	O4	H8	M2
E180a-d	O4	H9	M2
E181a-d	O5	H1	M2
E182a-d	O5	H2	M2
E183a-d	O5	H3	M2
E184a-d	O5	H4	M2
E185a-d	O5	H5	M2
E186a-d	O5	H6	M2
E187a-d	O5	H7	M2
E188a-d	O5	H8	M2
E189a-d	O5	H9	M2
E190a-d	O6	H1	M2
E191a-d	O6	H2	M2
E192a-d	O6	H3	M2
E193a-d	O6	H4	M2

Example	O Group	H Group	M Group
E194a-d	O6	H5	M2
E195a-d	O6	H6	M2
E196a-d	O6	H7	M2
E197a-d	O6	H8	M2
E198a-d	O6	H9	M2
E199a-d	O7	H1	M2
E200a-d	O7	H2	M2
E201a-d	O7	H3	M2
E202a-d	O7	H4	M2
E203a-d	O7	H5	M2
E204a-d	O7	H6	M2
E205a-d	O7	H7	M2
E206a-d	O7	H8	M2
E207a-d	O7	H9	M2
E208a-d	O8	H1	M2
E209a-d	O8	H2	M2
E210a-d	O8	H3	M2
E211a-d	O8	H4	M2
E212a-d	O8	H5	M2
E213a-d	O8	H6	M2
E214a-d	O8	H7	M2
E215a-d	O8	H8	M2
E216a-d	O8	H9	M2
E217a-d	O9	H1	M2
E218a-d	O9	H2	M2
E219a-d	O9	H3	M2
E220a-d	O9	H4	M2
E221a-d	O9	H5	M2
E222a-d	O9	H6	M2
E223a-d	O9	H7	M2
E224a-d	O9	H8	M2
E225a-d	O9	H9	M2
E226a-d	O10	H1	M2
E227a-d	O10	H2	M2
E228a-d	O10	H3	M2
E229a-d	O10	H4	M2
E230a-d	O10	H5	M2
E231a-d	O10	H6	M2
E232a-d	O10	H7	M2
E233a-d	O10	H8	M2
E234a-d	O10	H9	M2
E235a-d	O11	H1	M2
E236a-d	O11	H2	M2
E237a-d	O11	H3	M2

Example	O Group	H Group	M Group
E238a-d	O11	H4	M2
E239a-d	O11	H5	M2
E240a-d	O11	H6	M2
E241a-d	O11	H7	M2
E242a-d	O11	H8	M2
E243a-d	O11	H9	M2
E244a-d	O12	H1	M2
E245a-d	O12	H2	M2
E246a-d	O12	H3	M2
E247a-d	O12	H4	M2
E248a-d	O12	H5	M2
E249a-d	O12	H6	M2
E250a-d	O12	H7	M2
E251a-d	O12	H8	M2
E252a-d	O12	H9	M2
E253a-d	O13	H1	M2
E254a-d	O13	H2	M2
E255a-d	O13	H3	M2
E256a-d	O13	H4	M2
E257a-d	O13	H5	M2
E258a-d	O13	H6	M2
E259a-d	O13	H7	M2
E260a-d	O13	H8	M2
E261a-d	O13	H9	M2
E262a-d	O14	H1	M2
E263a-d	O14	H2	M2
E264a-d	O14	H3	M2
E265a-d	O14	H4	M2
E266a-d	O14	H5	M2
E267a-d	O14	H6	M2
E268a-d	O14	H7	M2
E269a-d	O14	H8	M2
E270a-d	O14	H9	M2
E271a-d	O15	H1	M2
E272a-d	O15	H2	M2
E273a-d	O15	H3	M2
E274a-d	O15	H4	M2
E275a-d	O15	H5	M2
E276a-d	O15	H6	M2
E277a-d	O15	H7	M2
E278a-d	O15	H8	M2
E279a-d	O15	H9	M2
E280a-d	O16	H1	M2
E281a-d	O16	H2	M2

Example	O Group	H Group	M Group
E282a-d	O16	H3	M2
E283a-d	O16	H4	M2
E284a-d	O16	H5	M2
E285a-d	O16	H6	M2
E286a-d	O16	H7	M2
E287a-d	O16	H8	M2
E288a-d	O16	H9	M2
E289a-d	O1	H1	M3
E290a-d	O1	H2	M3
E291a-d	O1	H3	M3
E292a-d	O1	H4	M3
E293a-d	O1	H5	M3
E294a-d	O1	H6	M3
E295a-d	O1	H7	M3
E296a-d	O1	H8	M3
E297a-d	O1	H9	M3
E298a-d	O2	H1	M3
E299a-d	O2	H2	M3
E300a-d	O2	H3	M3
E301a-d	O2	H4	M3
E302a-d	O2	H5	M3
E303a-d	O2	H6	M3
E304a-d	O2	H7	M3
E305a-d	O2	H8	M3
E306a-d	O2	H9	M3
E307a-d	O3	H1	M3
E308a-d	O3	H2	M3
E309a-d	O3	H3	M3
E310a-d	O3	H4	M3
E311a-d	O3	H5	M3
E312a-d	O3	H6	M3
E313a-d	O3	H7	M3
E314a-d	O3	H8	M3
E315a-d	O3	H9	M3
E316a-d	O4	H1	M3
E317a-d	O4	H2	M3
E318a-d	O4	H3	M3
E319a-d	O4	H4	M3
E320a-d	O4	H5	M3
E321a-d	O4	H6	M3
E322a-d	O4	H7	M3
E323a-d	O4	H8	M3
E324a-d	O4	H9	M3
E325a-d	O5	H1	M3

Example	O Group	H Group	M Group
E326a-d	O5	H2	M3
E327a-d	O5	H3	M3
E328a-d	O5	H4	M3
E329a-d	O5	H5	M3
E330a-d	O5	H6	M3
E331a-d	O5	H7	M3
E332a-d	O5	H8	M3
E333a-d	O5	H9	M3
E334a-d	O6	H1	M3
E335a-d	O6	H2	M3
E336a-d	O6	H3	M3
E337a-d	O6	H4	M3
E338a-d	O6	H5	M3
E339a-d	O6	H6	M3
E340a-d	O6	H7	M3
E341a-d	O6	H8	M3
E342a-d	O6	H9	M3
E343a-d	O7	H1	M3
E344a-d	O7	H2	M3
E345a-d	O7	H3	M3
E346a-d	O7	H4	M3
E347a-d	O7	H5	M3
E348a-d	O7	H6	M3
E349a-d	O7	H7	M3
E350a-d	O7	H8	M3
E351a-d	O7	H9	M3
E352a-d	O7	H1	M3
E353a-d	O8	H2	M3
E354a-d	O8	H3	M3
E355a-d	O8	H4	M3
E356a-d	O8	H5	M3
E357a-d	O8	H6	M3
E358a-d	O8	H7	M3
E359a-d	O8	H8	M3
E360a-d	O8	H9	M3
E361a-d	O9	H1	M3
E362a-d	O9	H2	M3
E363a-d	O9	H3	M3
E364a-d	O9	H4	M3
E365a-d	O9	H5	M3
E366a-d	O9	H6	M3
E367a-d	O9	H7	M3
E368a-d	O9	H8	M3
E369a-d	O9	H9	M3

Example	O Group	H Group	M Group
E370a-d	O10	H1	M3
E371a-d	O10	H2	M3
E372a-d	O10	H3	M3
E373a-d	O10	H4	M3
E374a-d	O10	H5	M3
E375a-d	O10	H6	M3
E376a-d	O10	H7	M3
E377a-d	O10	H8	M3
E378a-d	O10	H9	M3
E379a-d	O11	H1	M3
E380a-d	O11	H2	M3
E381a-d	O11	H3	M3
E382a-d	O11	H4	M3
E383a-d	O11	H5	M3
E384a-d	O11	H6	M3
E385a-d	O11	H7	M3
E386a-d	O11	H8	M3
E387a-d	O11	H9	M3
E388a-d	O12	H1	M3
E389a-d	O12	H2	M3
E390a-d	O12	H3	M3
E391a-d	O12	H4	M3
E392a-d	O12	H5	M3
E393a-d	O12	H6	M3
E394a-d	O12	H7	M3
E395a-d	O12	H8	M3
E396a-d	O12	H9	M3
E397a-d	O13	H1	M3
E398a-d	O13	H2	M3
E399a-d	O13	H3	M3
E400a-d	O13	H4	M3
E401a-d	O13	H5	M3
E402a-d	O13	H6	M3
E403a-d	O13	H7	M3
E404a-d	O13	H8	M3
E405a-d	O13	H9	M3
E406a-d	O14	H1	M3
E407a-d	O14	H2	M3
E408a-d	O14	H3	M3
E409a-d	O14	H4	M3
E410a-d	O14	H5	M3
E411a-d	O14	H6	M3
E412a-d	O14	H7	M3
E413a-d	O14	H8	M3

Example	O Group	H Group	M Group
E414a-d	O14	H9	M3
E415a-d	O15	H1	M3
E416a-d	O15	H2	M3
E417a-d	O15	H3	M3
E418a-d	O15	H4	M3
E419a-d	O15	H5	M3
E420a-d	O15	H6	M3
E421a-d	O15	H7	M3
E422a-d	O15	H8	M3
E423a-d	O15	H9	M3
E424a-d	O16	H1	M3
E425a-d	O16	H2	M3
E426a-d	O16	H3	M3
E427a-d	O16	H4	M3
E428a-d	O16	H5	M3
E429a-d	O16	H6	M3
E430a-d	O16	H7	M3
E431a-d	O16	H8	M3
E432a-d	O16	H9	M3
E433a-d	O1	H1	M4
E434a-d	O1	H2	M4
E435a-d	O1	H3	M4
E436a-d	O1	H4	M4
E437a-d	O1	H5	M4
E438a-d	O1	H6	M4
E439a-d	O1	H7	M4
E440a-d	O1	H8	M4
E441a-d	O1	H9	M4
E442a-d	O2	H1	M4
E443a-d	O2	H2	M4
E444a-d	O2	H3	M4
E445a-d	O2	H4	M4
E446a-d	O2	H5	M4
E447a-d	O2	H6	M4
E448a-d	O2	H7	M4
E449a-d	O2	H8	M4
E450a-d	O2	H9	M4
E451a-d	O3	H1	M4
E452a-d	O3	H2	M4
E453a-d	O3	H3	M4
E454a-d	O3	H4	M4
E455a-d	O3	H5	M4
E456a-d	O3	H6	M4
E457a-d	O3	H7	M4

Example	O Group	H Group	M Group
E458a-d	O3	H8	M4
E459a-d	O3	H9	M4
E460a-d	O4	H1	M4
E461a-d	O4	H2	M4
E462a-d	O4	H3	M4
E463a-d	O4	H4	M4
E464a-d	O4	H5	M4
E465a-d	O4	H6	M4
E466a-d	O4	H7	M4
E467a-d	O4	H8	M4
E468a-d	O4	H9	M4
E469a-d	O5	H1	M4
E470a-d	O5	H2	M4
E471a-d	O5	H3	M4
E472a-d	O5	H4	M4
E473a-d	O5	H5	M4
E474a-d	O5	H6	M4
E475a-d	O5	H7	M4
E476a-d	O5	H8	M4
E477a-d	O5	H9	M4
E478a-d	O6	H1	M4
E479a-d	O6	H2	M4
E480a-d	O6	H3	M4
E481a-d	O6	H4	M4
E482a-d	O6	H5	M4
E483a-d	O6	H6	M4
E484a-d	O6	H7	M4
E485a-d	O6	H8	M4
E486a-d	O6	H9	M4
E487a-d	O7	H1	M4
E488a-d	O7	H2	M4
E489a-d	O7	H3	M4
E490a-d	O7	H4	M4
E491a-d	O7	H5	M4
E492a-d	O7	H6	M4
E493a-d	O7	H7	M4
E494a-d	O7	H8	M4
E495a-d	O7	H9	M4
E496a-d	O8	H1	M4
E497a-d	O8	H2	M4
E498a-d	O8	H3	M4
E499a-d	O8	H4	M4
E500a-d	O8	H5	M4
E501a-d	O8	H6	M4

Example	O Group	H Group	M Group
E502a-d	O8	H7	M4
E503a-d	O8	H8	M4
E504a-d	O8	H9	M4
E505a-d	O9	H1	M4
E506a-d	O9	H2	M4
E507a-d	O9	H3	M4
E508a-d	O9	H4	M4
E509a-d	O9	H5	M4
E510a-d	O9	H6	M4
E511a-d	O9	H7	M4
E512a-d	O9	H8	M4
E513a-d	O9	H9	M4
E514a-d	O10	H1	M4
E515a-d	O10	H2	M4
E516a-d	O10	H3	M4
E517a-d	O10	H4	M4
E518a-d	O10	H5	M4
E519a-d	O10	H6	M4
E520a-d	O10	H7	M4
E521a-d	O10	H8	M4
E522a-d	O10	H9	M4
E523a-d	O11	H1	M4
E524a-d	O11	H2	M4
E525a-d	O11	H3	M4
E526a-d	O11	H4	M4
E527a-d	O11	H5	M4
E528a-d	O11	H6	M4
E529a-d	O11	H7	M4
E530a-d	O11	H8	M4
E531a-d	O11	H9	M4
E532a-d	O12	H1	M4
E533a-d	O12	H2	M4
E534a-d	O12	H3	M4
E535a-d	O12	H4	M4
E536a-d	O12	H5	M4
E537a-d	O12	H6	M4
E538a-d	O12	H7	M4
E539a-d	O12	H8	M4
E540a-d	O12	H9	M4
E541a-d	O13	H1	M4
E542a-d	O13	H2	M4
E543a-d	O13	H3	M4
E544a-d	O13	H4	M4
E545a-d	O13	H5	M4

Example	O Group	H Group	M Group
E546a-d	O13	H6	M4
E547a-d	O13	H7	M4
E548a-d	O13	H8	M4
E549a-d	O13	H9	M4
E550a-d	O14	H1	M4
E551a-d	O14	H2	M4
E552a-d	O14	H3	M4
E553a-d	O14	H4	M4
E554a-d	O14	H5	M4
E555a-d	O14	H6	M4
E556a-d	O14	H7	M4
E557a-d	O14	H8	M4
E558a-d	O14	H9	M4
E559a-d	O15	H1	M4
E560a-d	O15	H2	M4
E561a-d	O15	H3	M4
E562a-d	O15	H4	M4
E563a-d	O15	H5	M4
E564a-d	O15	H6	M4
E565a-d	O15	H7	M4
E566a-d	O15	H8	M4
E567a-d	O15	H9	M4
E568a-d	O16	H1	M4
E569a-d	O16	H2	M4
E570a-d	O16	H3	M4
E571a-d	O16	H4	M4
E572a-d	O16	H5	M4
E573a-d	O16	H6	M4
E574a-d	O16	H7	M4
E575a-d	O16	H8	M4
E576a-d	O16	H9	M4
E577a-d	O1	H1	M5
E578a-d	O1	H2	M5
E579a-d	O1	H3	M5
E580a-d	O1	H4	M5
E581a-d	O1	H5	M5
E582a-d	O1	H6	M5
E583a-d	O1	H7	M5
E584a-d	O1	H8	M5
E585a-d	O1	H9	M5
E586a-d	O2	H1	M5
E587a-d	O2	H2	M5
E588a-d	O2	H3	M5
E589a-d	O2	H4	M5

Example	O Group	H Group	M Group
E590a-d	O2	H5	M5
E591a-d	O2	H6	M5
E592a-d	O2	H7	M5
E593a-d	O2	H8	M5
E594a-d	O2	H9	M5
E595a-d	O3	H1	M5
E596a-d	O3	H2	M5
E597a-d	O3	H3	M5
E598a-d	O3	H4	M5
E599a-d	O3	H5	M5
E600a-d	O3	H6	M5
E601a-d	O3	H7	M5
E602a-d	O3	H8	M5
E603a-d	O3	H9	M5
E604a-d	O4	H1	M5
E605a-d	O4	H2	M5
E606a-d	O4	H3	M5
E607a-d	O4	H4	M5
E608a-d	O4	H5	M5
E609a-d	O4	H6	M5
E610a-d	O4	H7	M5
E611a-d	O4	H8	M5
E612a-d	O4	H9	M5
E613a-d	O5	H1	M5
E614a-d	O5	H2	M5
E615a-d	O5	H3	M5
E616a-d	O5	H4	M5
E617a-d	O5	H5	M5
E618a-d	O5	H6	M5
E619a-d	O5	H7	M5
E620a-d	O5	H8	M5
E621a-d	O5	H9	M5
E622a-d	O6	H1	M5
E623a-d	O6	H2	M5
E624a-d	O6	H3	M5
E625a-d	O6	H4	M5
E626a-d	O6	H5	M5
E627a-d	O6	H6	M5
E628a-d	O6	H7	M5
E629a-d	O6	H8	M5
E630a-d	O6	H9	M5
E631a-d	O7	H1	M5
E632a-d	O7	H2	M5
E633a-d	O7	H3	M5

Example	O Group	H Group	M Group
E634a-d	O7	H4	M5
E635a-d	O7	H5	M5
E636a-d	O7	H6	M5
E637a-d	O7	H7	M5
E638a-d	O7	H8	M5
E639a-d	O7	H9	M5
E640a-d	O8	H1	M5
E641a-d	O8	H2	M5
E642a-d	O8	H3	M5
E643a-d	O8	H4	M5
E644a-d	O8	H5	M5
E645a-d	O8	H6	M5
E646a-d	O8	H7	M5
E647a-d	O8	H8	M5
E648a-d	O8	H9	M5
E649a-d	O9	H1	M5
E650a-d	O9	H2	M5
E651a-d	O9	H3	M5
E652a-d	O9	H4	M5
E653a-d	O9	H5	M5
E654a-d	O9	H6	M5
E655a-d	O9	H7	M5
E656a-d	O9	H8	M5
E657a-d	O9	H9	M5
E658a-d	O10	H1	M5
E659a-d	O10	H2	M5
E660a-d	O10	H3	M5
E661a-d	O10	H4	M5
E662a-d	O10	H5	M5
E663a-d	O10	H6	M5
E664a-d	O10	H7	M5
E665a-d	O10	H8	M5
E666a-d	O10	H9	M5
E667a-d	O11	H1	M5
E668a-d	O11	H2	M5
E669a-d	O11	H3	M5
E670a-d	O11	H4	M5
E671a-d	O11	H5	M5
E672a-d	O11	H6	M5
E673a-d	O11	H7	M5
E674a-d	O11	H8	M5
E675a-d	O11	H9	M5
E676a-d	O12	H1	M5
E677a-d	O12	H2	M5

Example	O Group	H Group	M Group
E678a-d	O12	H3	M5
E679a-d	O12	H4	M5
E680a-d	O12	H5	M5
E681a-d	O12	H6	M5
E682a-d	O12	H7	M5
E683a-d	O12	H8	M5
E684a-d	O12	H9	M5
E685a-d	O13	H1	M5
E686a-d	O13	H2	M5
E687a-d	O13	H3	M5
E688a-d	O13	H4	M5
E689a-d	O13	H5	M5
E690a-d	O13	H6	M5
E691a-d	O13	H7	M5
E692a-d	O13	H8	M5
E693a-d	O13	H9	M5
E694a-d	O14	H1	M5
E695a-d	O14	H2	M5
E696a-d	O14	H3	M5
E697a-d	O14	H4	M5
E698a-d	O14	H5	M5
E699a-d	O14	H6	M5
E700a-d	O14	H7	M5
E701a-d	O14	H8	M5
E702a-d	O14	H9	M5
E703a-d	O15	H1	M5
E704a-d	O15	H2	M5
E705a-d	O15	H3	M5
E706a-d	O15	H4	M5
E707a-d	O15	H5	M5
E708a-d	O15	H6	M5
E709a-d	O15	H7	M5
E710a-d	O15	H8	M5
E711a-d	O15	H9	M5
E712a-d	O16	H1	M5
E713a-d	O16	H2	M5
E714a-d	O16	H3	M5
E715a-d	O16	H4	M5
E716a-d	O16	H5	M5
E717a-d	O16	H6	M5
E718a-d	O16	H7	M5
E719a-d	O16	H8	M5
E720a-d	O16	H9	M5
E721a-d	O1	H1	M6

Example	O Group	H Group	M Group
E722a-d	O1	H2	M6
E723a-d	O1	H3	M6
E724a-d	O1	H4	M6
E725a-d	O1	H5	M6
E726a-d	O1	H6	M6
E727a-d	O1	H7	M6
E728a-d	O1	H8	M6
E729a-d	O1	H9	M6
E730a-d	O2	H1	M6
E731a-d	O2	H2	M6
E732a-d	O2	H3	M6
E733a-d	O2	H4	M6
E734a-d	O2	H5	M6
E735a-d	O2	H6	M6
E736a-d	O2	H7	M6
E737a-d	O2	H8	M6
E738a-d	O2	H9	M6
E739a-d	O3	H1	M6
E740a-d	O3	H2	M6
E741a-d	O3	H3	M6
E742a-d	O3	H4	M6
E743a-d	O3	H5	M6
E744a-d	O3	H6	M6
E745a-d	O3	H7	M6
E746a-d	O3	H8	M6
E747a-d	O3	H9	M6
E748a-d	O4	H1	M6
E749a-d	O4	H2	M6
E750a-d	O4	H3	M6
E751a-d	O4	H4	M6
E752a-d	O4	H5	M6
E753a-d	O4	H6	M6
E754a-d	O4	H7	M6
E755a-d	O4	H8	M6
E756a-d	O4	H9	M6
E757a-d	O5	H1	M6
E758a-d	O5	H2	M6
E759a-d	O5	H3	M6
E760a-d	O5	H4	M6
E761a-d	O5	H5	M6
E762a-d	O5	H6	M6
E763a-d	O5	H7	M6
E764a-d	O5	H8	M6
E765a-d	O5	H9	M6

Example	O Group	H Group	M Group
E766a-d	O6	H1	M6
E767a-d	O6	H2	M6
E768a-d	O6	H3	M6
E769a-d	O6	H4	M6
E770a-d	O6	H5	M6
E771a-d	O6	H6	M6
E772a-d	O6	H7	M6
E773a-d	O6	H8	M6
E774a-d	O6	H9	M6
E775a-d	O7	H1	M6
E776a-d	O7	H2	M6
E777a-d	O7	H3	M6
E778a-d	O7	H4	M6
E779a-d	O7	H5	M6
E780a-d	O7	H6	M6
E781a-d	O7	H7	M6
E782a-d	O7	H8	M6
E783a-d	O7	H9	M6
E784a-d	O8	H1	M6
E785a-d	O8	H2	M6
E786a-d	O8	H3	M6
E787a-d	O8	H4	M6
E788a-d	O8	H5	M6
E789a-d	O8	H6	M6
E790a-d	O8	H7	M6
E791a-d	O8	H8	M6
E792a-d	O8	H9	M6
E793a-d	O9	H1	M6
E794a-d	O9	H2	M6
E795a-d	O9	H3	M6
E796a-d	O9	H4	M6
E797a-d	O9	H5	M6
E798a-d	O9	H6	M6
E799a-d	O9	H7	M6
E800a-d	O9	H8	M6
E801a-d	O9	H9	M6
E802a-d	O10	H1	M6
E803a-d	O10	H2	M6
E804a-d	O10	H3	M6
E805a-d	O10	H4	M6
E806a-d	O10	H5	M6
E807a-d	O10	H6	M6
E808a-d	O10	H7	M6
E809a-d	O10	H8	M6

Example	O Group	H Group	M Group
E810a-d	O10	H9	M6
E811a-d	O11	H1	M6
E812a-d	O11	H2	M6
E813a-d	O11	H3	M6
E814a-d	O11	H4	M6
E815a-d	O11	H5	M6
E816a-d	O11	H6	M6
E817a-d	O11	H7	M6
E818a-d	O11	H8	M6
E819a-d	O11	H9	M6
E820a-d	O12	H1	M6
E821a-d	O12	H2	M6
E822a-d	O12	H3	M6
E823a-d	O12	H4	M6
E824a-d	O12	H5	M6
E825a-d	O12	H6	M6
E826a-d	O12	H7	M6
E827a-d	O12	H8	M6
E828a-d	O12	H9	M6
E829a-d	O13	H1	M6
E830a-d	O13	H2	M6
E831a-d	O13	H3	M6
E832a-d	O13	H4	M6
E833a-d	O13	H5	M6
E834a-d	O13	H6	M6
E835a-d	O13	H7	M6
E836a-d	O13	H8	M6
E837a-d	O13	H9	M6
E838a-d	O14	H1	M6
E839a-d	O14	H2	M6
E840a-d	O14	H3	M6
E841a-d	O14	H4	M6
E842a-d	O14	H5	M6
E843a-d	O14	H6	M6
E844a-d	O14	H7	M6
E845a-d	O14	H8	M6
E846a-d	O14	H9	M6
E847a-d	O15	H1	M6
E848a-d	O15	H2	M6
E849a-d	O15	H3	M6
E850a-d	O15	H4	M6
E851a-d	O15	H5	M6
E852a-d	O15	H6	M6
E853a-d	O15	H7	M6

Example	O Group	H Group	M Group
E854a-d	O15	H8	M6
E855a-d	O15	H9	M6
E856a-d	O16	H1	M6
E857a-d	O16	H2	M6
E858a-d	O16	H3	M6
E859a-d	O16	H4	M6
E860a-d	O16	H5	M6
E861a-d	O16	H6	M6
E862a-d	O16	H7	M6
E863a-d	O16	H8	M6
E864a-d	O16	H9	M6
E865a-d	O1	H1	M7
E866a-d	O1	H2	M7
E867a-d	O1	H3	M7
E868a-d	O1	H4	M7
E869a-d	O1	H5	M7
E870a-d	O1	H6	M7
E871a-d	O1	H7	M7
E872a-d	O1	H8	M7
E873a-d	O1	H9	M7
E874a-d	O2	H1	M7
E875a-d	O2	H2	M7
E876a-d	O2	H3	M7
E877a-d	O2	H4	M7
E878a-d	O2	H5	M7
E879a-d	O2	H6	M7
E880a-d	O2	H7	M7
E881a-d	O2	H8	M7
E882a-d	O2	H9	M7
E883a-d	O3	H1	M7
E884a-d	O3	H2	M7
E885a-d	O3	H3	M7
E886a-d	O3	H4	M7
E887a-d	O3	H5	M7
E888a-d	O3	H6	M7
E889a-d	O3	H7	M7
E890a-d	O3	H8	M7
E891a-d	O3	H9	M7
E892a-d	O4	H1	M7
E893a-d	O4	H2	M7
E894a-d	O4	H3	M7
E895a-d	O4	H4	M7
E896a-d	O4	H5	M7
E897a-d	O4	H6	M7

Example	O Group	H Group	M Group
E898a-d	O4	H7	M7
E899a-d	O4	H8	M7
E900a-d	O4	H9	M7
E901a-d	O5	H1	M7
E902a-d	O5	H2	M7
E903a-d	O5	H3	M7
E904a-d	O5	H4	M7
E905a-d	O5	H5	M7
E906a-d	O5	H6	M7
E907a-d	O5	H7	M7
E908a-d	O5	H8	M7
E909a-d	O5	H9	M7
E910a-d	O6	H1	M7
E911a-d	O6	H2	M7
E912a-d	O6	H3	M7
E913a-d	O6	H4	M7
E914a-d	O6	H5	M7
E915a-d	O6	H6	M7
E916a-d	O6	H7	M7
E917a-d	O6	H8	M7
E918a-d	O6	H9	M7
E919a-d	O7	H1	M7
E920a-d	O7	H2	M7
E921a-d	O7	H3	M7
E922a-d	O7	H4	M7
E923a-d	O7	H5	M7
E924a-d	O7	H6	M7
E925a-d	O7	H7	M7
E926a-d	O7	H8	M7
E927a-d	O7	H9	M7
E928a-d	O8	H1	M7
E929a-d	O8	H2	M7
E930a-d	O8	H3	M7
E931a-d	O8	H4	M7
E932a-d	O8	H5	M7
E933a-d	O8	H6	M7
E934a-d	O8	H7	M7
E935a-d	O8	H8	M7
E936a-d	O8	H9	M7
E937a-d	O9	H1	M7
E938a-d	O9	H2	M7
E939a-d	O9	H3	M7
E940a-d	O9	H4	M7
E941a-d	O9	H5	M7

Example	O Group	H Group	M Group
E942a-d	O9	H6	M7
E943a-d	O9	H7	M7
E944a-d	O9	H8	M7
E945a-d	O9	H9	M7
E946a-d	O10	H1	M7
E947a-d	O10	H2	M7
E948a-d	O10	H3	M7
E949a-d	O10	H4	M7
E950a-d	O10	H5	M7
E951a-d	O10	H6	M7
E952a-d	O10	H7	M7
E953a-d	O10	H8	M7
E954a-d	O10	H9	M7
E955a-d	O11	H1	M7
E956a-d	O11	H2	M7
E957a-d	O11	H3	M7
E958a-d	O11	H4	M7
E959a-d	O11	H5	M7
E960a-d	O11	H6	M7
E961a-d	O11	H7	M7
E962a-d	O11	H8	M7
E963a-d	O11	H9	M7
E964a-d	O12	H1	M7
E965a-d	O12	H2	M7
E966a-d	O12	H3	M7
E967a-d	O12	H4	M7
E968a-d	O12	H5	M7
E969a-d	O12	H6	M7
E970a-d	O12	H7	M7
E971a-d	O12	H8	M7
E972a-d	O12	H9	M7
E973a-d	O13	H1	M7
E974a-d	O13	H2	M7
E975a-d	O13	H3	M7
E976a-d	O13	H4	M7
E977a-d	O13	H5	M7
E978a-d	O13	H6	M7
E979a-d	O13	H7	M7
E980a-d	O13	H8	M7
E981a-d	O13	H9	M7
E982a-d	O14	H1	M7
E983a-d	O14	H2	M7
E984a-d	O14	H3	M7
E985a-d	O14	H4	M7

Example	O Group	H Group	M Group
E986a-d	O14	H5	M7
E987a-d	O14	H6	M7
E988a-d	O14	H7	M7
E989a-d	O14	H8	M7
E990a-d	O14	H9	M7
E991a-d	O15	H1	M7
E992a-d	O15	H2	M7
E993a-d	O15	H3	M7
E994a-d	O15	H4	M7
E995a-d	O15	H5	M7
E996a-d	O15	H6	M7
E997a-d	O15	H7	M7
E998a-d	O15	H8	M7
E999a-d	O15	H9	M7
E1000a-d	O16	H1	M7
E1001a-d	O16	H2	M7
E1002a-d	O16	H3	M7
E1003a-d	O16	H4	M7
E1004a-d	O16	H5	M7
E1005a-d	O16	H6	M7
E1006a-d	O16	H7	M7
E1007a-d	O16	H8	M7
E1008a-d	O16	H9	M7
E1009a-d	O1	H1	M8
E1010a-d	O1	H2	M8
E1011a-d	O1	H3	M8
E1012a-d	O1	H4	M8
E1013a-d	O1	H5	M8
E1014a-d	O1	H6	M8
E1015a-d	O1	H7	M8
E1016a-d	O1	H8	M8
E1017a-d	O1	H9	M8
E1018a-d	O2	H1	M8
E1019a-d	O2	H2	M8
E1020a-d	O2	H3	M8
E1021a-d	O2	H4	M8
E1022a-d	O2	H5	M8
E1023a-d	O2	H6	M8
E1024a-d	O2	H7	M8
E1025a-d	O2	H8	M8
E1026a-d	O2	H9	M8
E1027a-d	O3	H1	M8
E1028a-d	O3	H2	M8
E1029a-d	O3	H3	M8

Example	O Group	H Group	M Group
E1030a-d	O3	H4	M8
E1031a-d	O3	H5	M8
E1032a-d	O3	H6	M8
E1033a-d	O3	H7	M8
E1034a-d	O3	H8	M8
E1035a-d	O3	H9	M8
E1036a-d	O4	H1	M8
E1037a-d	O4	H2	M8
E1038a-d	O4	H3	M8
E1039a-d	O4	H4	M8
E1040a-d	O4	H5	M8
E1041a-d	O4	H6	M8
E1042a-d	O4	H7	M8
E1043a-d	O4	H8	M8
E1044a-d	O4	H9	M8
E1045a-d	O5	H1	M8
E1046a-d	O5	H2	M8
E1047a-d	O5	H3	M8
E1048a-d	O5	H4	M8
E1049a-d	O5	H5	M8
E1050a-d	O5	H6	M8
E1051a-d	O5	H7	M8
E1052a-d	O5	H8	M8
E1053a-d	O5	H9	M8
E1054a-d	O6	H1	M8
E1055a-d	O6	H2	M8
E1056a-d	O6	H3	M8
E1057a-d	O6	H4	M8
E1058a-d	O6	H5	M8
E1059a-d	O6	H6	M8
E1060a-d	O6	H7	M8
E1061a-d	O6	H8	M8
E1062a-d	O6	H9	M8
E1063a-d	O7	H1	M8
E1064a-d	O7	H2	M8
E1065a-d	O7	H3	M8
E1066a-d	O7	H4	M8
E1067a-d	O7	H5	M8
E1068a-d	O7	H6	M8
E1069a-d	O7	H7	M8
E1070a-d	O7	H8	M8
E1071a-d	O7	H9	M8
E1072a-d	O8	H1	M8
E1073a-d	O8	H2	M8

Example	O Group	H Group	M Group
E1074a-d	O8	H3	M8
E1075a-d	O8	H4	M8
E1076a-d	O8	H5	M8
E1077a-d	O8	H6	M8
E1078a-d	O8	H7	M8
E1079a-d	O8	H8	M8
E1080a-d	O8	H9	M8
E1081a-d	O9	H1	M8
E1082a-d	O9	H2	M8
E1083a-d	O9	H3	M8
E1084a-d	O9	H4	M8
E1085a-d	O9	H5	M8
E1086a-d	O9	H6	M8
E1087a-d	O9	H7	M8
E1088a-d	O9	H8	M8
E1089a-d	O9	H9	M8
E1090a-d	O10	H1	M8
E1091a-d	O10	H2	M8
E1092a-d	O10	H3	M8
E1093a-d	O10	H4	M8
E1094a-d	O10	H5	M8
E1095a-d	O10	H6	M8
E1096a-d	O10	H7	M8
E1097a-d	O10	H8	M8
E1098a-d	O10	H9	M8
E1099a-d	O11	H1	M8
E1100a-d	O11	H2	M8
E1101a-d	O11	H3	M8
E1102a-d	O11	H4	M8
E1103a-d	O11	H5	M8
E1104a-d	O11	H6	M8
E1105a-d	O11	H7	M8
E1106a-d	O11	H8	M8
E1107a-d	O11	H9	M8
E1108a-d	O12	H1	M8
E1109a-d	O12	H2	M8
E1110a-d	O12	H3	M8
E1111a-d	O12	H4	M8
E1112a-d	O12	H5	M8
E1113a-d	O12	H6	M8
E1114a-d	O12	H7	M8
E1115a-d	O12	H8	M8
E1116a-d	O12	H9	M8
E1117a-d	O13	H1	M8

Example	O Group	H Group	M Group
E1118a-d	O13	H2	M8
E1119a-d	O13	H3	M8
E1120a-d	O13	H4	M8
E1121a-d	O13	H5	M8
E1122a-d	O13	H6	M8
E1123a-d	O13	H7	M8
E1124a-d	O13	H8	M8
E1125a-d	O13	H9	M8
E1126a-d	O14	H1	M8
E1127a-d	O14	H2	M8
E1128a-d	O14	H3	M8
E1129a-d	O14	H4	M8
E1130a-d	O14	H5	M8
E1131a-d	O14	H6	M8
E1132a-d	O14	H7	M8
E1133a-d	O14	H8	M8
E1134a-d	O14	H9	M8
E1135a-d	O15	H1	M8
E1136a-d	O15	H2	M8
E1137a-d	O15	H3	M8
E1138a-d	O15	H4	M8
E1139a-d	O15	H5	M8
E1140a-d	O15	H6	M8
E1141a-d	O15	H7	M8
E1142a-d	O15	H8	M8
E1143a-d	O15	H9	M8
E1144a-d	O16	H1	M8
E1145a-d	O16	H2	M8
E1146a-d	O16	H3	M8
E1147a-d	O16	H4	M8
E1148a-d	O16	H5	M8
E1149a-d	O16	H6	M8
E1150a-d	O16	H7	M8
E1151a-d	O16	H8	M8
E1152a-d	O16	H9	M8
E1153a-d	O1	H1	M9
E1154a-d	O1	H2	M9
E1155a-d	O1	H3	M9
E1156a-d	O1	H4	M9
E1157a-d	O1	H5	M9
E1158a-d	O1	H6	M9
E1159a-d	O1	H7	M9
E1160a-d	O1	H8	M9
E1161a-d	O1	H9	M9

Example	O Group	H Group	M Group
E1162a-d	O2	H1	M9
E1163a-d	O2	H2	M9
E1164a-d	O2	H3	M9
E1165a-d	O2	H4	M9
E1166a-d	O2	H5	M9
E1167a-d	O2	H6	M9
E1168a-d	O2	H7	M9
E1169a-d	O2	H8	M9
E1170a-d	O2	H9	M9
E1171a-d	O3	H1	M9
E1172a-d	O3	H2	M9
E1173a-d	O3	H3	M9
E1174a-d	O3	H4	M9
E1175a-d	O3	H5	M9
E1176a-d	O3	H6	M9
E1177a-d	O3	H7	M9
E1178a-d	O3	H8	M9
E1179a-d	O3	H9	M9
E1180a-d	O4	H1	M9
E1181a-d	O4	H2	M9
E1182a-d	O4	H3	M9
E1183a-d	O4	H4	M9
E1184a-d	O4	H5	M9
E1185a-d	O4	H6	M9
E1186a-d	O4	H7	M9
E1187a-d	O4	H8	M9
E1188a-d	O4	H9	M9
E1189a-d	O5	H1	M9
E1190a-d	O5	H2	M9
E1191a-d	O5	H3	M9
E1192a-d	O5	H4	M9
E1193a-d	O5	H5	M9
E1194a-d	O5	H6	M9
E1195a-d	O5	H7	M9
E1196a-d	O5	H8	M9
E1197a-d	O5	H9	M9
E1198a-d	O6	H1	M9
E1199a-d	O6	H2	M9
E1200a-d	O6	H3	M9
E1201a-d	O6	H4	M9
E1202a-d	O6	H5	M9
E1203a-d	O6	H6	M9
E1204a-d	O6	H7	M9
E1205a-d	O6	H8	M9

Example	O Group	H Group	M Group
E1206a-d	O6	H9	M9
E1207a-d	O7	H1	M9
E1208a-d	O7	H2	M9
E1209a-d	O7	H3	M9
E1210a-d	O7	H4	M9
E1211a-d	O7	H5	M9
E1212a-d	O7	H6	M9
E1213a-d	O7	H7	M9
E1214a-d	O7	H8	M9
E1215a-d	O7	H9	M9
E1216a-d	O8	H1	M9
E1217a-d	O8	H2	M9
E1218a-d	O8	H3	M9
E1219a-d	O8	H4	M9
E1220a-d	O8	H5	M9
E1221a-d	O8	H6	M9
E1222a-d	O8	H7	M9
E1223a-d	O8	H8	M9
E1224a-d	O8	H9	M9
E1225a-d	O9	H1	M9
E1226a-d	O9	H2	M9
E1227a-d	O9	H3	M9
E1228a-d	O9	H4	M9
E1229a-d	O9	H5	M9
E1230a-d	O9	H6	M9
E1231a-d	O9	H7	M9
E1232a-d	O9	H8	M9
E1233a-d	O9	H9	M9
E1234a-d	O10	H1	M9
E1235a-d	O10	H2	M9
E1236a-d	O10	H3	M9
E1237a-d	O10	H4	M9
E1238a-d	O10	H5	M9
E1239a-d	O10	H6	M9
E1240a-d	O10	H7	M9
E1241a-d	O10	H8	M9
E1242a-d	O10	H9	M9
E1243a-d	O11	H1	M9
E1244a-d	O11	H2	M9
E1245a-d	O11	H3	M9
E1246a-d	O11	H4	M9
E1247a-d	O11	H5	M9
E1248a-d	O11	H6	M9
E1249a-d	O11	H7	M9

Example	O Group	H Group	M Group
E1250a-d	O11	H8	M9
E1251a-d	O11	H9	M9
E1252a-d	O12	H1	M9
E1253a-d	O12	H2	M9
E1254a-d	O12	H3	M9
E1255a-d	O12	H4	M9
E1256a-d	O12	H5	M9
E1257a-d	O12	H6	M9
E1258a-d	O12	H7	M9
E1259a-d	O12	H8	M9
E1260a-d	O12	H9	M9
E1261a-d	O13	H1	M9
E1262a-d	O13	H2	M9
E1263a-d	O13	H3	M9
E1264a-d	O13	H4	M9
E1265a-d	O13	H5	M9
E1266a-d	O13	H6	M9
E1267a-d	O13	H7	M9
E1268a-d	O13	H8	M9
E1269a-d	O13	H9	M9
E1270a-d	O14	H1	M9
E1271a-d	O14	H2	M9
E1272a-d	O14	H3	M9
E1273a-d	O14	H4	M9
E1274a-d	O14	H5	M9
E1275a-d	O14	H6	M9
E1276a-d	O14	H7	M9
E1277a-d	O14	H8	M9
E1278a-d	O14	H9	M9
E1279a-d	O15	H1	M9
E1280a-d	O15	H2	M9
E1281a-d	O15	H3	M9
E1282a-d	O15	H4	M9
E1283a-d	O15	H5	M9
E1284a-d	O15	H6	M9
E1285a-d	O15	H7	M9
E1286a-d	O15	H8	M9
E1287a-d	O15	H9	M9
E1288a-d	O16	H1	M9
E1289a-d	O16	H2	M9
E1290a-d	O16	H3	M9
E1291a-d	O16	H4	M9
E1292a-d	O16	H5	M9
E1293a-d	O16	H6	M9

Example	O Group	H Group	M Group
E1294a-d	O16	H7	M9
E1295a-d	O16	H8	M9
E1296a-d	O16	H9	M9
E1297a-d	O1	H1	M10
E1298a-d	O1	H2	M10
E1299a-d	O1	H3	M10
E1300a-d	O1	H4	M10
E1301a-d	O1	H5	M10
E1302a-d	O1	H6	M10
E1303a-d	O1	H7	M10
E1304a-d	O1	H8	M10
E1305a-d	O1	H9	M10
E1306a-d	O2	H1	M10
E1307a-d	O2	H2	M10
E1308a-d	O2	H3	M10
E1309a-d	O2	H4	M10
E1310a-d	O2	H5	M10
E1311a-d	O2	H6	M10
E1312a-d	O2	H7	M10
E1313a-d	O2	H8	M10
E1314a-d	O2	H9	M10
E1315a-d	O3	H1	M10
E1316a-d	O3	H2	M10
E1317a-d	O3	H3	M10
E1318a-d	O3	H4	M10
E1319a-d	O3	H5	M10
E1320a-d	O3	H6	M10
E1321a-d	O3	H7	M10
E1322a-d	O3	H8	M10
E1323a-d	O3	H9	M10
E1324a-d	O4	H1	M10
E1325a-d	O4	H2	M10
E1326a-d	O4	H3	M10
E1327a-d	O4	H4	M10
E1328a-d	O4	H5	M10
E1329a-d	O4	H6	M10
E1330a-d	O4	H7	M10
E1331a-d	O4	H8	M10
E1332a-d	O4	H9	M10
E1333a-d	O5	H1	M10
E1334a-d	O5	H2	M10
E1335a-d	O5	H3	M10
E1336a-d	O5	H4	M10
E1337a-d	O5	H5	M10

Example	O Group	H Group	M Group
E1338a-d	O5	H6	M10
E1339a-d	O5	H7	M10
E1340a-d	O5	H8	M10
E1341a-d	O5	H9	M10
E1342a-d	O6	H1	M10
E1343a-d	O6	H2	M10
E1344a-d	O6	H3	M10
E1345a-d	O6	H4	M10
E1346a-d	O6	H5	M10
E1347a-d	O6	H6	M10
E1348a-d	O6	H7	M10
E1349a-d	O6	H8	M10
E1350a-d	O6	H9	M10
E1351a-d	O7	H1	M10
E1352a-d	O7	H2	M10
E1353a-d	O7	H3	M10
E1354a-d	O7	H4	M10
E1355a-d	O7	H5	M10
E1356a-d	O7	H6	M10
E1357a-d	O7	H7	M10
E1358a-d	O7	H8	M10
E1359a-d	O7	H9	M10
E1360a-d	O8	H1	M10
E1361a-d	O8	H2	M10
E1362a-d	O8	H3	M10
E1363a-d	O8	H4	M10
E1364a-d	O8	H5	M10
E1365a-d	O8	H6	M10
E1366a-d	O8	H7	M10
E1367a-d	O8	H8	M10
E1368a-d	O8	H9	M10
E1369a-d	O9	H1	M10
E1370a-d	O9	H2	M10
E1371a-d	O9	H3	M10
E1372a-d	O9	H4	M10
E1373a-d	O9	H5	M10
E1374a-d	O9	H6	M10
E1375a-d	O9	H7	M10
E1376a-d	O9	H8	M10
E1377a-d	O9	H9	M10
E1378a-d	O10	H1	M10
E1379a-d	O10	H2	M10
E1380a-d	O10	H3	M10
E1381a-d	O10	H4	M10

Example	O Group	H Group	M Group
E1382a-d	O10	H5	M10
E1383a-d	O10	H6	M10
E1384a-d	O10	H7	M10
E1385a-d	O10	H8	M10
E1386a-d	O10	H9	M10
E1387a-d	O11	H1	M10
E1388a-d	O11	H2	M10
E1389a-d	O11	H3	M10
E1390a-d	O11	H4	M10
E1391a-d	O11	H5	M10
E1392a-d	O11	H6	M10
E1393a-d	O11	H7	M10
E1394a-d	O11	H8	M10
E1395a-d	O11	H9	M10
E1396a-d	O12	H1	M10
E1397a-d	O12	H2	M10
E1398a-d	O12	H3	M10
E1399a-d	O12	H4	M10
E1400a-d	O12	H5	M10
E1401a-d	O12	H6	M10
E1402a-d	O12	H7	M10
E1403a-d	O12	H8	M10
E1404a-d	O12	H9	M10
E1405a-d	O13	H1	M10
E1406a-d	O13	H2	M10
E1407a-d	O13	H3	M10
E1408a-d	O13	H4	M10
E1409a-d	O13	H5	M10
E1410a-d	O13	H6	M10
E1411a-d	O13	H7	M10
E1412a-d	O13	H8	M10
E1413a-d	O13	H9	M10
E1414a-d	O14	H1	M10
E1415a-d	O14	H2	M10
E1416a-d	O14	H3	M10
E1417a-d	O14	H4	M10
E1418a-d	O14	H5	M10
E1419a-d	O14	H6	M10
E1420a-d	O14	H7	M10
E1421a-d	O14	H8	M10
E1422a-d	O14	H9	M10
E1423a-d	O15	H1	M10
E1424a-d	O15	H2	M10
E1425a-d	O15	H3	M10

Example	O Group	H Group	M Group
E1426a-d	O15	H4	M10
E1427a-d	O15	H5	M10
E1428a-d	O15	H6	M10
E1429a-d	O15	H7	M10
E1430a-d	O15	H8	M10
E1431a-d	O15	H9	M10
E1432a-d	O16	H1	M10
E1433a-d	O16	H2	M10
E1434a-d	O16	H3	M10
E1435a-d	O16	H4	M10
E1436a-d	O16	H5	M10
E1437a-d	O16	H6	M10
E1438a-d	O16	H7	M10
E1439a-d	O16	H8	M10
E1440a-d	O16	H9	M10
E1441a-d	O1	H1	M11
E1442a-d	O1	H2	M11
E1443a-d	O1	H3	M11
E1444a-d	O1	H4	M11
E1445a-d	O1	H5	M11
E1446a-d	O1	H6	M11
E1447a-d	O1	H7	M11
E1448a-d	O1	H8	M11
E1449a-d	O1	H9	M11
E1450a-d	O2	H1	M11
E1451a-d	O2	H2	M11
E1452a-d	O2	H3	M11
E1453a-d	O2	H4	M11
E1454a-d	O2	H5	M11
E1455a-d	O2	H6	M11
E1456a-d	O2	H7	M11
E1457a-d	O2	H8	M11
E1458a-d	O2	H9	M11
E1459a-d	O3	H1	M11
E1460a-d	O3	H2	M11
E1461a-d	O3	H3	M11
E1462a-d	O3	H4	M11
E1463a-d	O3	H5	M11
E1464a-d	O3	H6	M11
E1465a-d	O3	H7	M11
E1466a-d	O3	H8	M11
E1467a-d	O3	H9	M11
E1468a-d	O4	H1	M11
E1469a-d	O4	H2	M11

Example	O Group	H Group	M Group
E1470a-d	O4	H3	M11
E1471a-d	O4	H4	M11
E1472a-d	O4	H5	M11
E1473a-d	O4	H6	M11
E1474a-d	O4	H7	M11
E1475a-d	O4	H8	M11
E1476a-d	O4	H9	M11
E1477a-d	O5	H1	M11
E1478a-d	O5	H2	M11
E1479a-d	O5	H3	M11
E1480a-d	O5	H4	M11
E1481a-d	O5	H5	M11
E1482a-d	O5	H6	M11
E1483a-d	O5	H7	M11
E1484a-d	O5	H8	M11
E1485a-d	O5	H9	M11
E1486a-d	O6	H1	M11
E1487a-d	O6	H2	M11
E1488a-d	O6	H3	M11
E1489a-d	O6	H4	M11
E1490a-d	O6	H5	M11
E1491a-d	O6	H6	M11
E1492a-d	O6	H7	M11
E1493a-d	O6	H8	M11
E1494a-d	O6	H9	M11
E1495a-d	O7	H1	M11
E1496a-d	O7	H2	M11
E1497a-d	O7	H3	M11
E1498a-d	O7	H4	M11
E1499a-d	O7	H5	M11
E1500a-d	O7	H6	M11
E1501a-d	O7	H7	M11
E1502a-d	O7	H8	M11
E1503a-d	O7	H9	M11
E1504a-d	O8	H1	M11
E1505a-d	O8	H2	M11
E1506a-d	O8	H3	M11
E1507a-d	O8	H4	M11
E1508a-d	O8	H5	M11
E1509a-d	O8	H6	M11
E1510a-d	O8	H7	M11
E1511a-d	O8	H8	M11
E1512a-d	O8	H9	M11
E1513a-d	O9	H1	M11

Example	O Group	H Group	M Group
E1514a-d	O9	H2	M11
E1515a-d	O9	H3	M11
E1516a-d	O9	H4	M11
E1517a-d	O9	H5	M11
E1518a-d	O9	H6	M11
E1519a-d	O9	H7	M11
E1520a-d	O9	H8	M11
E1521a-d	O9	H9	M11
E1522a-d	O10	H1	M11
E1523a-d	O10	H2	M11
E1524a-d	O10	H3	M11
E1525a-d	O10	H4	M11
E1526a-d	O10	H5	M11
E1527a-d	O10	H6	M11
E1528a-d	O10	H7	M11
E1529a-d	O10	H8	M11
E1530a-d	O10	H9	M11
E1531a-d	O11	H1	M11
E1532a-d	O11	H2	M11
E1533a-d	O11	H3	M11
E1534a-d	O11	H4	M11
E1535a-d	O11	H5	M11
E1536a-d	O11	H6	M11
E1537a-d	O11	H7	M11
E1538a-d	O11	H8	M11
E1539a-d	O11	H9	M11
E1540a-d	O12	H1	M11
E1541a-d	O12	H2	M11
E1542a-d	O12	H3	M11
E1543a-d	O12	H4	M11
E1544a-d	O12	H5	M11
E1545a-d	O12	H6	M11
E1546a-d	O12	H7	M11
E1547a-d	O12	H8	M11
E1548a-d	O12	H9	M11
E1549a-d	O13	H1	M11
E1550a-d	O13	H2	M11
E1551a-d	O13	H3	M11
E1552a-d	O13	H4	M11
E1553a-d	O13	H5	M11
E1554a-d	O13	H6	M11
E1555a-d	O13	H7	M11
E1556a-d	O13	H8	M11
E1557a-d	O13	H9	M11

Example	O Group	H Group	M Group
E1558a-d	O14	H1	M11
E1559a-d	O14	H2	M11
E1560a-d	O14	H3	M11
E1561a-d	O14	H4	M11
E1562a-d	O14	H5	M11
E1563a-d	O14	H6	M11
E1564a-d	O14	H7	M11
E1565a-d	O14	H8	M11
E1566a-d	O14	H9	M11
E1567a-d	O15	H1	M11
E1568a-d	O15	H2	M11
E1569a-d	O15	H3	M11
E1570a-d	O15	H4	M11
E1571a-d	O15	H5	M11
E1572a-d	O15	H6	M11
E1573a-d	O15	H7	M11
E1574a-d	O15	H8	M11
E1575a-d	O15	H9	M11
E1576a-d	O16	H1	M11
E1577a-d	O16	H2	M11
E1578a-d	O16	H3	M11
E1579a-d	O16	H4	M11
E1580a-d	O16	H5	M11
E1581a-d	O16	H6	M11
E1582a-d	O16	H7	M11
E1583a-d	O16	H8	M11
E1584a-d	O16	H9	M11
E1585a-d	O1	H1	M12
E1586a-d	O1	H2	M12
E1587a-d	O1	H3	M12
E1588a-d	O1	H4	M12
E1589a-d	O1	H5	M12
E1590a-d	O1	H6	M12
E1591a-d	O1	H7	M12
E1592a-d	O1	H8	M12
E1593a-d	O1	H9	M12
E1594a-d	O2	H1	M12
E1595a-d	O2	H2	M12
E1596a-d	O2	H3	M12
E1597a-d	O2	H4	M12
E1598a-d	O2	H5	M12
E1599a-d	O2	H6	M12
E1600a-d	O2	H7	M12
E1601a-d	O2	H8	M12

Example	O Group	H Group	M Group
E1602a-d	O2	H9	M12
E1603a-d	O3	H1	M12
E1604a-d	O3	H2	M12
E1605a-d	O3	H3	M12
E1606a-d	O3	H4	M12
E1607a-d	O3	H5	M12
E1608a-d	O3	H6	M12
E1609a-d	O3	H7	M12
E1610a-d	O3	H8	M12
E1611a-d	O3	H9	M12
E1612a-d	O4	H1	M12
E1613a-d	O4	H2	M12
E1614a-d	O4	H3	M12
E1615a-d	O4	H4	M12
E1616a-d	O4	H5	M12
E1617a-d	O4	H6	M12
E1618a-d	O4	H7	M12
E1619a-d	O4	H8	M12
E1620a-d	O4	H9	M12
E1621a-d	O5	H1	M12
E1622a-d	O5	H2	M12
E1623a-d	O5	H3	M12
E1624a-d	O5	H4	M12
E1625a-d	O5	H5	M12
E1626a-d	O5	H6	M12
E1627a-d	O5	H7	M12
E1628a-d	O5	H8	M12
E1629a-d	O5	H9	M12
E1630a-d	O6	H1	M12
E1631a-d	O6	H2	M12
E1632a-d	O6	H3	M12
E1633a-d	O6	H4	M12
E1634a-d	O6	H5	M12
E1635a-d	O6	H6	M12
E1636a-d	O6	H7	M12
E1637a-d	O6	H8	M12
E1638a-d	O6	H9	M12
E1639a-d	O7	H1	M12
E1640a-d	O7	H2	M12
E1641a-d	O7	H3	M12
E1642a-d	O7	H4	M12
E1643a-d	O7	H5	M12
E1644a-d	O7	H6	M12
E1645a-d	O7	H7	M12

Example	O Group	H Group	M Group
E1646a-d	O7	H8	M12
E1647a-d	O7	H9	M12
E1648a-d	O8	H1	M12
E1649a-d	O8	H2	M12
E1650a-d	O8	H3	M12
E1651a-d	O8	H4	M12
E1652a-d	O8	H5	M12
E1653a-d	O8	H6	M12
E1654a-d	O8	H7	M12
E1655a-d	O8	H8	M12
E1656a-d	O8	H9	M12
E1657a-d	O9	H1	M12
E1658a-d	O9	H2	M12
E1659a-d	O9	H3	M12
E1660a-d	O9	H4	M12
E1661a-d	O9	H5	M12
E1662a-d	O9	H6	M12
E1663a-d	O9	H7	M12
E1664a-d	O9	H8	M12
E1665a-d	O9	H9	M12
E1666a-d	O10	H1	M12
E1667a-d	O10	H2	M12
E1668a-d	O10	H3	M12
E1669a-d	O10	H4	M12
E1670a-d	O10	H5	M12
E1671a-d	O10	H6	M12
E1672a-d	O10	H7	M12
E1673a-d	O10	H8	M12
E1674a-d	O10	H9	M12
E1675a-d	O11	H1	M12
E1676a-d	O11	H2	M12
E1677a-d	O11	H3	M12
E1678a-d	O11	H4	M12
E1679a-d	O11	H5	M12
E1680a-d	O11	H6	M12
E1681a-d	O11	H7	M12
E1682a-d	O11	H8	M12
E1683a-d	O11	H9	M12
E1684a-d	O12	H1	M12
E1685a-d	O12	H2	M12
E1686a-d	O12	H3	M12
E1687a-d	O12	H4	M12
E1688a-d	O12	H5	M12
E1689a-d	O12	H6	M12

Example	O Group	H Group	M Group
E1690a-d	O12	H7	M12
E1691a-d	O12	H8	M12
E1692a-d	O12	H9	M12
E1693a-d	O13	H1	M12
E1694a-d	O13	H2	M12
E1695a-d	O13	H3	M12
E1696a-d	O13	H4	M12
E1697a-d	O13	H5	M12
E1698a-d	O13	H6	M12
E1699a-d	O13	H7	M12
E1700a-d	O13	H8	M12
E1701a-d	O13	H9	M12
E1702a-d	O14	H1	M12
E1703a-d	O14	H2	M12
E1704a-d	O14	H3	M12
E1705a-d	O14	H4	M12
E1706a-d	O14	H5	M12
E1707a-d	O14	H6	M12
E1708a-d	O14	H7	M12
E1709a-d	O14	H8	M12
E1710a-d	O14	H9	M12
E1711a-d	O15	H1	M12
E1712a-d	O15	H2	M12
E1713a-d	O15	H3	M12
E1714a-d	O15	H4	M12
E1715a-d	O15	H5	M12
E1716a-d	O15	H6	M12
E1717a-d	O15	H7	M12
E1718a-d	O15	H8	M12
E1719a-d	O15	H9	M12
E1720a-d	O16	H1	M12
E1721a-d	O16	H2	M12
E1722a-d	O16	H3	M12
E1723a-d	O16	H4	M12
E1724a-d	O16	H5	M12
E1725a-d	O16	H6	M12
E1726a-d	O16	H7	M12
E1727a-d	O16	H8	M12
E1728a-d	O16	H9	M12
E1729a-d	O1	H1	M13
E1730a-d	O1	H2	M13
E1731a-d	O1	H3	M13
E1732a-d	O1	H4	M13
E1733a-d	O1	H5	M13

Example	O Group	H Group	M Group
E1734a-d	O1	H6	M13
E1735a-d	O1	H7	M13
E1736a-d	O1	H8	M13
E1737a-d	O1	H9	M13
E1738a-d	O2	H1	M13
E1739a-d	O2	H2	M13
E1740a-d	O2	H3	M13
E1741a-d	O2	H4	M13
E1742a-d	O2	H5	M13
E1743a-d	O2	H6	M13
E1744a-d	O2	H7	M13
E1745a-d	O2	H8	M13
E1746a-d	O2	H9	M13
E1747a-d	O3	H1	M13
E1748a-d	O3	H2	M13
E1749a-d	O3	H3	M13
E1750a-d	O3	H4	M13
E1751a-d	O3	H5	M13
E1752a-d	O3	H6	M13
E1753a-d	O3	H7	M13
E1754a-d	O3	H8	M13
E1755a-d	O3	H9	M13
E1756a-d	O4	H1	M13
E1757a-d	O4	H2	M13
E1758a-d	O4	H3	M13
E1759a-d	O4	H4	M13
E1760a-d	O4	H5	M13
E1761a-d	O4	H6	M13
E1762a-d	O4	H7	M13
E1763a-d	O4	H8	M13
E1764a-d	O4	H9	M13
E1765a-d	O5	H1	M13
E1766a-d	O5	H2	M13
E1767a-d	O5	H3	M13
E1768a-d	O5	H4	M13
E1769a-d	O5	H5	M13
E1770a-d	O5	H6	M13
E1771a-d	O5	H7	M13
E1772a-d	O5	H8	M13
E1773a-d	O5	H9	M13
E1774a-d	O6	H1	M13
E1775a-d	O6	H2	M13
E1776a-d	O6	H3	M13
E1777a-d	O6	H4	M13

Example	O Group	H Group	M Group
E1778a-d	O6	H5	M13
E1779a-d	O6	H6	M13
E1780a-d	O6	H7	M13
E1781a-d	O6	H8	M13
E1782a-d	O6	H9	M13
E1783a-d	O7	H1	M13
E1784a-d	O7	H2	M13
E1785a-d	O7	H3	M13
E1786a-d	O7	H4	M13
E1787a-d	O7	H5	M13
E1788a-d	O7	H6	M13
E1789a-d	O7	H7	M13
E1790a-d	O7	H8	M13
E1791a-d	O7	H9	M13
E1792a-d	O8	H1	M13
E1793a-d	O8	H2	M13
E1794a-d	O8	H3	M13
E1795a-d	O8	H4	M13
E1796a-d	O8	H5	M13
E1797a-d	O8	H6	M13
E1798a-d	O8	H7	M13
E1799a-d	O8	H8	M13
E1800a-d	O8	H9	M13
E1801a-d	O9	H1	M13
E1802a-d	O9	H2	M13
E1803a-d	O9	H3	M13
E1804a-d	O9	H4	M13
E1805a-d	O9	H5	M13
E1806a-d	O9	H6	M13
E1807a-d	O9	H7	M13
E1808a-d	O9	H8	M13
E1809a-d	O9	H9	M13
E1810a-d	O10	H1	M13
E1811a-d	O10	H2	M13
E1812a-d	O10	H3	M13
E1813a-d	O10	H4	M13
E1814a-d	O10	H5	M13
E1815a-d	O10	H6	M13
E1816a-d	O10	H7	M13
E1817a-d	O10	H8	M13
E1818a-d	O10	H9	M13
E1819a-d	O11	H1	M13
E1820a-d	O11	H2	M13
E1821a-d	O11	H3	M13

Example	O Group	H Group	M Group
E1822a-d	O11	H4	M13
E1823a-d	O11	H5	M13
E1824a-d	O11	H6	M13
E1825a-d	O11	H7	M13
E1826a-d	O11	H8	M13
E1827a-d	O11	H9	M13
E1828a-d	O12	H1	M13
E1829a-d	O12	H2	M13
E1830a-d	O12	H3	M13
E1831a-d	O12	H4	M13
E1832a-d	O12	H5	M13
E1833a-d	O12	H6	M13
E1834a-d	O12	H7	M13
E1835a-d	O12	H8	M13
E1836a-d	O12	H9	M13
E1837a-d	O13	H1	M13
E1838a-d	O13	H2	M13
E1839a-d	O13	H3	M13
E1840a-d	O13	H4	M13
E1841a-d	O13	H5	M13
E1842a-d	O13	H6	M13
E1843a-d	O13	H7	M13
E1844a-d	O13	H8	M13
E1845a-d	O13	H9	M13
E1846a-d	O14	H1	M13
E1847a-d	O14	H2	M13
E1848a-d	O14	H3	M13
E1849a-d	O14	H4	M13
E1850a-d	O14	H5	M13
E1851a-d	O14	H6	M13
E1852a-d	O14	H7	M13 M13
E1853a-d	O14	H8	M13
E1854a-d	O14	H9	M13
E1855a-d	O15	H1	M13
E1856a-d	O15	H2	M13
E1857a-d	O15	H3	M13
E1858a-d	O15	H4	M13
E1859a-d	O15	H5	M13
E1860a-d	O15	H6	M13
E1861a-d	O15	H7	M13
E1862a-d	O15	H8	M13
E1863a-d	O15	H9	M13
E1864a-d	O16	H1	M13
E1865a-d	O16	H2	M13

Example	O Group	H Group	M Group
E1866a-d	O16	H3	M13
E1867a-d	O16	H4	M13
E1868a-d	O16	H5	M13
E1869a-d	O16	H6	M13
E1870a-d	O16	H7	M13
E1871a-d	O16	H8	M13
E1872a-d	O16	H9	M13
E1873a-d	O1	H1	M14
E1874a-d	O1	H2	M14
E1875a-d	O1	H3	M14
E1876a-d	O1	H4	M14
E1877a-d	O1	H5	M14
E1878a-d	O1	H6	M14
E1879a-d	O1	H7	M14
E1880a-d	O1	H8	M14
E1881a-d	O1	H9	M14
E1882a-d	O2	H1	M14
E1883a-d	O2	H2	M14
E1884a-d	O2	H3	M14
E1885a-d	O2	H4	M14
E1886a-d	O2	H5	M14
E1887a-d	O2	H6	M14
E1888a-d	O2	H7	M14
E1889a-d	O2	H8	M14
E1890a-d	O2	H9	M14
E1891a-d	O3	H1	M14
E1892a-d	O3	H2	M14
E1893a-d	O3	H3	M14
E1894a-d	O3	H4	M14
E1895a-d	O3	H5	M14
E1896a-d	O3	H6	M14
E1897a-d	O3	H7	M14
E1898a-d	O3	H8	M14
E1899a-d	O3	H9	M14
E1900a-d	O4	H1	M14
E1901a-d	O4	H2	M14
E1902a-d	O4	H3	M14
E1903a-d	O4	H4	M14
E1904a-d	O4	H5	M14
E1905a-d	O4	H6	M14
E1906a-d	O4	H7	M14
E1907a-d	O4	H8	M14
E1908a-d	O4	H9	M14
E1909a-d	O5	H1	M14

Example	O Group	H Group	M Group
E1910a-d	O5	H2	M14
E1911a-d	O5	H3	M14
E1912a-d	O5	H4	M14
E1913a-d	O5	H5	M14
E1914a-d	O5	H6	M14
E1915a-d	O5	H7	M14
E1916a-d	O5	H8	M14
E1917a-d	O5	H9	M14
E1918a-d	O6	H1	M14
E1919a-d	O6	H2	M14
E1920a-d	O6	H3	M14
E1921a-d	O6	H4	M14
E1922a-d	O6	H5	M14
E1923a-d	O6	H6	M14
E1924a-d	O6	H7	M14
E1925a-d	O6	H8	M14
E1926a-d	O6	H9	M14
E1927a-d	O7	H1	M14
E1928a-d	O7	H2	M14
E1929a-d	O7	H3	M14
E1930a-d	O7	H4	M14
E1931a-d	O7	H5	M14
E1932a-d	O7	H6	M14
E1933a-d	O7	H7	M14
E1934a-d	O7	H8	M14
E1935a-d	O7	H9	M14
E1936a-d	O8	H1	M14
E1937a-d	O8	H2	M14
E1938a-d	O8	H3	M14
E1939a-d	O8	H4	M14
E1940a-d	O8	H5	M14
E1941a-d	O8	H6	M14
E1942a-d	O8	H7	M14
E1943a-d	O8	H8	M14
E1944a-d	O8	H9	M14
E1945a-d	O9	H1	M14
E1946a-d	O9	H2	M14
E1947a-d	O9	H3	M14
E1948a-d	O9	H4	M14
E1949a-d	O9	H5	M14
E1950a-d	O9	H6	M14
E1951a-d	O9	H7	M14
E1952a-d	O9	H8	M14
E1953a-d	O9	H9	M14

Example	O Group	H Group	M Group
E1954a-d	O10	H1	M14
E1955a-d	O10	H2	M14
E1956a-d	O10	H3	M14
E1957a-d	O10	H4	M14
E1958a-d	O10	H5	M14
E1959a-d	O10	H6	M14
E1960a-d	O10	H7	M14
E1961a-d	O10	H8	M14
E1962a-d	O10	H9	M14
E1963a-d	O11	H1	M14
E1964a-d	O11	H2	M14
E1965a-d	O11	H3	M14
E1966a-d	O11	H4	M14
E1967a-d	O11	H5	M14
E1968a-d	O11	H6	M14
E1969a-d	O11	H7	M14
E1970a-d	O11	H8	M14
E1971a-d	O11	H9	M14
E1972a-d	O12	H1	M14
E1973a-d	O12	H2	M14
E1974a-d	O12	H3	M14
E1975a-d	O12	H4	M14
E1976a-d	O12	H5	M14
E1977a-d	O12	H6	M14
E1978a-d	O12	H7	M14
E1979a-d	O12	H8	M14
E1980a-d	O12	H9	M14
E1981a-d	O13	H1	M14
E1982a-d	O13	H2	M14
E1983a-d	O13	H3	M14
E1984a-d	O13	H4	M14
E1985a-d	O13	H5	M14
E1986a-d	O13	H6	M14
E1987a-d	O13	H7	M14
E1988a-d	O13	H8	M14
E1989a-d	O13	H9	M14
E1990a-d	O14	H1	M14
E1991a-d	O14	H2	M14
E1992a-d	O14	H3	M14
E1993a-d	O14	H4	M14
E1994a-d	O14	H5	M14
E1995a-d	O14	H6	M14
E1996a-d	O14	H7	M14
E1997a-d	O14	H8	M14

Example	O Group	H Group	M Group
E1998a-d	O14	H9	M14
E1999a-d	O15	H1	M14
E2000a-d	O15	H2	M14
E2001a-d	O15	H3	M14
E2002a-d	O15	H4	M14
E2003a-d	O15	H5	M14
E2004a-d	O15	H6	M14
E2005a-d	O15	H7	M14
E2006a-d	O15	H8	M14
E2007a-d	O15	H9	M14
E2008a-d	O16	H1	M14
E2009a-d	O16	H2	M14
E2010a-d	O16	H3	M14
E2011a-d	O16	H4	M14
E2012a-d	O16	H5	M14
E2013a-d	O16	H6	M14
E2014a-d	O16	H7	M14
E2015a-d	O16	H8	M14
E2016a-d	O16	H9	M14
E2017a-d	O1	H1	M15
E2018a-d	O1	H2	M15
E2019a-d	O1	H3	M15
E2020a-d	O1	H4	M15
E2021a-d	O1	H5	M15
E2022a-d	O1	H6	M15
E2023a-d	O1	H7	M15
E2024a-d	O1	H8	M15
E2025a-d	O1	H9	M15
E2026a-d	O2	H1	M15
E2027a-d	O2	H2	M15
E2028a-d	O2	H3	M15
E2029a-d	O2	H4	M15
E2030a-d	O2	H5	M15
E2031a-d	O2	H6	M15
E2032a-d	O2	H7	M15
E2033a-d	O2	H8	M15
E2034a-d	O2	H9	M15
E2035a-d	O3	H1	M15
E2036a-d	O3	H2	M15
E2037a-d	O3	H3	M15
E2038a-d	O3	H4	M15
E2039a-d	O3	H5	M15
E2040a-d	O3	H6	M15
E2041a-d	O3	H7	M15

Example	O Group	H Group	M Group
E2042a-d	O3	H8	M15
E2043a-d	O3	H9	M15
E2044a-d	O4	H1	M15
E2045a-d	O4	H2	M15
E2046a-d	O4	H3	M15
E2047a-d	O4	H4	M15
E2048a-d	O4	H5	M15
E2049a-d	O4	H6	M15
E2050a-d	O4	H7	M15
E2051a-d	O4	H8	M15
E2052a-d	O4	H9	M15
E2053a-d	O5	H1	M15
E2054a-d	O5	H2	M15
E2055a-d	O5	H3	M15
E2056a-d	O5	H4	M15
E2057a-d	O5	H5	M15
E2058a-d	O5	H6	M15
E2059a-d	O5	H7	M15
E2060a-d	O5	H8	M15
E2061a-d	O5	H9	M15
E2062a-d	O6	H1	M15
E2063a-d	O6	H2	M15
E2064a-d	O6	H3	M15
E2065a-d	O6	H4	M15
E2066a-d	O6	H5	M15
E2067a-d	O6	H6	M15
E2068a-d	O6	H7	M15
E2069a-d	O6	H8	M15
E2070a-d	O6	H9	M15
E2071a-d	O7	H1	M15
E2072a-d	O7	H2	M15
E2073a-d	O7	H3	M15
E2074a-d	O7	H4	M15
E2075a-d	O7	H5	M15
E2076a-d	O7	H6	M15
E2077a-d	O7	H7	M15
E2078a-d	O7	H8	M15
E2079a-d	O7	H9	M15
E2080a-d	O8	H1	M15
E2081a-d	O8	H2	M15
E2082a-d	O8	H3	M15
E2083a-d	O8	H4	M15
E2084a-d	O8	H5	M15
E2085a-d	O8	H6	M15

Example	O Group	H Group	M Group
E2086a-d	O8	H7	M15
E2087a-d	O8	H8	M15
E2088a-d	O8	H9	M15
E2089a-d	O9	H1	M15
E2090a-d	O9	H2	M15
E2091a-d	O9	H3	M15
E2092a-d	O9	H4	M15
E2093a-d	O9	H5	M15
E2094a-d	O9	H6	M15
E2095a-d	O9	H7	M15
E2096a-d	O9	H8	M15
E2097a-d	O9	H9	M15
E2098a-d	O10	H1	M15
E2099a-d	O10	H2	M15
E2100a-d	O10	H3	M15
E2101a-d	O10	H4	M15
E2102a-d	O10	H5	M15
E2103a-d	O10	H6	M15
E2104a-d	O10	H7	M15
E2105a-d	O10	H8	M15
E2106a-d	O10	H9	M15
E2107a-d	O11	H1	M15
E2108a-d	O11	H2	M15
E2109a-d	O11	H3	M15
E2110a-d	O11	H4	M15
E2111a-d	O11	H5	M15
E2112a-d	O11	H6	M15
E2113a-d	O11	H7	M15
E2114a-d	O11	H8	M15
E2115a-d	O11	H9	M15
E2116a-d	O12	H1	M15
E2117a-d	O12	H2	M15
E2118a-d	O12	H3	M15
E2119a-d	O12	H4	M15
E2120a-d	O12	H5	M15
E2121a-d	O12	H6	M15
E2122a-d	O12	H7	M15
E2123a-d	O12	H8	M15
E2124a-d	O12	H9	M15
E2125a-d	O13	H1	M15
E2126a-d	O13	H2	M15
E2127a-d	O13	H3	M15
E2128a-d	O13	H4	M15
E2129a-d	O13	H5	M15

Example	O Group	H Group	M Group
E2130a-d	O13	H6	M15
E2131a-d	O13	H7	M15
E2132a-d	O13	H8	M15
E2133a-d	O13	H9	M15
E2134a-d	O14	H1	M15
E2135a-d	O14	H2	M15
E2136a-d	O14	H3	M15
E2137a-d	O14	H4	M15
E2138a-d	O14	H5	M15
E2139a-d	O14	H6	M15
E2140a-d	O14	H7	M15
E2141a-d	O14	H8	M15
E2142a-d	O14	H9	M15
E2143a-d	O15	H1	M15
E2144a-d	O15	H2	M15
E2145a-d	O15	H3	M15
E2146a-d	O15	H4	M15
E2147a-d	O15	H5	M15
E2148a-d	O15	H6	M15
E2149a-d	O15	H7	M15
E2150a-d	O15	H8	M15
E2151a-d	O15	H9	M15
E2152a-d	O16	H1	M15
E2153a-d	O16	H2	M15
E2154a-d	O16	H3	M15
E2155a-d	O16	H4	M15
E2156a-d	O16	H5	M15
E2157a-d	O16	H6	M15
E2158a-d	O16	H7	M15
E2159a-d	O16	H8	M15
E2160a-d	O16	H9	M15
E2161a-d	O1	H1	M16
E2162a-d	O1	H2	M16
E2163a-d	O1	H3	M16
E2164a-d	O1	H4	M16
E2165a-d	O1	H5	M16
E2166a-d	O1	H6	M16
E2167a-d	O1	H7	M16
E2168a-d	O1	H8	M16
E2169a-d	O1	H9	M16
E2170a-d	O2	H1	M16
E2171a-d	O2	H2	M16
E2172a-d	O2	H3	M16
E2173a-d	O2	H4	M16

Example	O Group	H Group	M Group
E2174a-d	O2	H5	M16
E2175a-d	O2	H6	M16
E2176a-d	O2	H7	M16
E2177a-d	O2	H8	M16
E2178a-d	O2	H9	M16
E2179a-d	O3	H1	M16
E2180a-d	O3	H2	M16
E2181a-d	O3	H3	M16
E2182a-d	O3	H4	M16
E2183a-d	O3	H5	M16
E2184a-d	O3	H6	M16
E2185a-d	O3	H7	M16
E2186a-d	O3	H8	M16
E2187a-d	O3	H9	M16
E2188a-d	O4	H1	M16
E2189a-d	O4	H2	M16
E2190a-d	O4	H3	M16
E2191a-d	O4	H4	M16
E2192a-d	O4	H5	M16
E2193a-d	O4	H6	M16
E2194a-d	O4	H7	M16
E2195a-d	O4	H8	M16
E2196a-d	O4	H9	M16
E2197a-d	O5	H1	M16
E2198a-d	O5	H2	M16
E2199a-d	O5	H3	M16
E2200a-d	O5	H4	M16
E2201a-d	O5	H5	M16
E2202a-d	O5	H6	M16
E2203a-d	O5	H7	M16
E2204a-d	O5	H8	M16
E2205a-d	O5	H9	M16
E2206a-d	O6	H1	M16
E2207a-d	O6	H2	M16
E2208a-d	O6	H3	M16
E2209a-d	O6	H4	M16
E2210a-d	O6	H5	M16
E2211a-d	O6	H6	M16
E2212a-d	O6	H7	M16
E2213a-d	O6	H8	M16
E2214a-d	O6	H9	M16
E2215a-d	O7	H1	M16
E2216a-d	O7	H2	M16
E2217a-d	O7	H3	M16

Example	O Group	H Group	M Group
E2218a-d	O7	H4	M16
E2219a-d	O7	H5	M16
E2220a-d	O7	H6	M16
E2221a-d	O7	H7	M16
E2222a-d	O7	H8	M16
E2223a-d	O7	H9	M16
E2224a-d	O8	H1	M16
E2225a-d	O8	H2	M16
E2226a-d	O8	H3	M16
E2227a-d	O8	H4	M16
E2228a-d	O8	H5	M16
E2229a-d	O8	H6	M16
E2230a-d	O8	H7	M16
E2231a-d	O8	H8	M16
E2232a-d	O8	H9	M16
E2233a-d	O9	H1	M16
E2234a-d	O9	H2	M16
E2235a-d	O9	H3	M16
E2236a-d	O9	H4	M16
E2237a-d	O9	H5	M16
E2238a-d	O9	H6	M16
E2239a-d	O9	H7	M16
E2240a-d	O9	H8	M16
E2241a-d	O9	H9	M16
E2242a-d	O10	H1	M16
E2243a-d	O10	H2	M16
E2244a-d	O10	H3	M16
E2245a-d	O10	H4	M16
E2246a-d	O10	H5	M16
E2247a-d	O10	H6	M16
E2248a-d	O10	H7	M16
E2249a-d	O10	H8	M16
E2250a-d	O10	H9	M16
E2251a-d	O11	H1	M16
E2252a-d	O11	H2	M16
E2253a-d	O11	H3	M16
E2254a-d	O11	H4	M16
E2255a-d	O11	H5	M16
E2256a-d	O11	H6	M16
E2257a-d	O11	H7	M16
E2258a-d	O11	H8	M16
E2259a-d	O11	H9	M16
E2260a-d	O12	H1	M16
E2261a-d	O12	H2	M16

Example	O Group	H Group	M Group
E2262a-d	O12	H3	M16
E2263a-d	O12	H4	M16
E2264a-d	O12	H5	M16
E2265a-d	O12	H6	M16
E2266a-d	O12	H7	M16
E2267a-d	O12	H8	M16
E2268a-d	O12	H9	M16
E2269a-d	O13	H1	M16
E2270a-d	O13	H2	M16
E2271a-d	O13	H3	M16
E2272a-d	O13	H4	M16
E2273a-d	O13	H5	M16
E2274a-d	O13	H6	M16
E2275a-d	O13	H7	M16
E2276a-d	O13	H8	M16
E2277a-d	O13	H9	M16
E2278a-d	O14	H1	M16
E2279a-d	O14	H2	M16
E2280a-d	O14	H3	M16
E2281a-d	O14	H4	M16
E2282a-d	O14	H5	M16
E2283a-d	O14	H6	M16
E2284a-d	O14	H7	M16
E2285a-d	O14	H8	M16
E2286a-d	O14	H9	M16
E2287a-d	O15	H1	M16
E2288a-d	O15	H2	M16
E2289a-d	O15	H3	M16
E2290a-d	O15	H4	M16
E2291a-d	O15	H5	M16
E2292a-d	O15	H6	M16
E2293a-d	O15	H7	M16
E2294a-d	O15	H8	M16
E2295a-d	O15	H9	M16
E2296a-d	O16	H1	M16
E2297a-d	O16	H2	M16
E2298a-d	O16	H3	M16
E2299a-d	O16	H4	M16
E2300a-d	O16	H5	M16
E2301a-d	O16	H6	M16
E2302a-d	O16	H7	M16
E2303a-d	O16	H8	M16
E2304a-d	O16	H9	M16
E2305a-d	O1	H1	M17

Example	O Group	H Group	M Group
E2306a-d	O1	H2	M17
E2307a-d	O1	H3	M17
E2308a-d	O1	H4	M17
E2309a-d	O1	H5	M17
E2310a-d	O1	H6	M17
E2311a-d	O1	H7	M17
E2312a-d	O1	H8	M17
E2313a-d	O1	H9	M17
E2314a-d	O2	H1	M17
E2315a-d	O2	H2	M17
E2316a-d	O2	H3	M17
E2317a-d	O2	H4	M17
E2318a-d	O2	H5	M17
E2319a-d	O2	H6	M17
E2320a-d	O2	H7	M17
E2321a-d	O2	H8	M17
E2322a-d	O2	H9	M17
E2323a-d	O3	H1	M17
E2324a-d	O3	H2	M17
E2325a-d	O3	H3	M17
E2326a-d	O3	H4	M17
E2327a-d	O3	H5	M17
E2328a-d	O3	H6	M17
E2329a-d	O3	H7	M17
E2330a-d	O3	H8	M17
E2331a-d	O3	H9	M17
E2332a-d	O4	H1	M17
E2333a-d	O4	H2	M17
E2334a-d	O4	H3	M17
E2335a-d	O4	H4	M17
E2336a-d	O4	H5	M17
E2337a-d	O4	H6	M17
E2338a-d	O4	H7	M17
E2339a-d	O4	H8	M17
E2340a-d	O4	H9	M17
E2341a-d	O5	H1	M17
E2342a-d	O5	H2	M17
E2343a-d	O5	H3	M17
E2344a-d	O5	H4	M17
E2345a-d	O5	H5	M17
E2346a-d	O5	H6	M17
E2347a-d	O5	H7	M17
E2348a-d	O5	H8	M17
E2349a-d	O5	H9	M17

Example	O Group	H Group	M Group
E2350a-d	O6	H1	M17
E2351a-d	O6	H2	M17
E2352a-d	O6	H3	M17
E2353a-d	O6	H4	M17
E2354a-d	O6	H5	M17
E2355a-d	O6	H6	M17
E2356a-d	O6	H7	M17
E2357a-d	O6	H8	M17
E2358a-d	O6	H9	M17
E2359a-d	O7	H1	M17
E2360a-d	O7	H2	M17
E2361a-d	O7	H3	M17
E2362a-d	O7	H4	M17
E2363a-d	O7	H5	M17
E2364a-d	O7	H6	M17
E2365a-d	O7	H7	M17
E2366a-d	O7	H8	M17
E2367a-d	O7	H9	M17
E2368a-d	O8	H1	M17
E2369a-d	O8	H2	M17
E2370a-d	O8	H3	M17
E2371a-d	O8	H4	M17
E2372a-d	O8	H5	M17
E2373a-d	O8	H6	M17
E2374a-d	O8	H7	M17
E2375a-d	O8	H8	M17
E2376a-d	O8	H9	M17
E2377a-d	O9	H1	M17
E2378a-d	O9	H2	M17
E2379a-d	O9	H3	M17
E2380a-d	O9	H4	M17
E2381a-d	O9	H5	M17
E2382a-d	O9	H6	M17
E2383a-d	O9	H7	M17
E2384a-d	O9	H8	M17
E2385a-d	O9	H9	M17
E2386a-d	O10	H1	M17
E2387a-d	O10	H2	M17
E2388a-d	O10	H3	M17
E2389a-d	O10	H4	M17
E2390a-d	O10	H5	M17
E2391a-d	O10	H6	M17
E2392a-d	O10	H7	M17
E2393a-d	O10	H8	M17

Example	O Group	H Group	M Group
E2394a-d	O10	H9	M17
E2395a-d	O11	H1	M17
E2396a-d	O11	H2	M17
E2397a-d	O11	H3	M17
E2398a-d	O11	H4	M17
E2399a-d	O11	H5	M17
E2400a-d	O11	H6	M17
E2401a-d	O11	H7	M17
E2402a-d	O11	H8	M17
E2403a-d	O11	H9	M17
E2404a-d	O12	H1	M17
E2405a-d	O12	H2	M17
E2406a-d	O12	H3	M17
E2407a-d	O12	H4	M17
E2408a-d	O12	H5	M17
E2409a-d	O12	H6	M17
E2410a-d	O12	H7	M17
E2411a-d	O12	H8	M17
E2412a-d	O12	H9	M17
E2413a-d	O13	H1	M17
E2414a-d	O13	H2	M17
E2415a-d	O13	H3	M17
E2416a-d	O13	H4	M17
E2417a-d	O13	H5	M17
E2418a-d	O13	H6	M17
E2419a-d	O13	H7	M17
E2420a-d	O13	H8	M17
E2421a-d	O13	H9	M17
E2422a-d	O14	H1	M17
E2423a-d	O14	H2	M17
E2424a-d	O14	H3	M17
E2425a-d	O14	H4	M17
E2426a-d	O14	H5	M17
E2427a-d	O14	H6	M17
E2428a-d	O14	H7	M17
E2429a-d	O14	H8	M17
E2430a-d	O14	H9	M17
E2431a-d	O15	H1	M17
E2432a-d	O15	H2	M17
E2433a-d	O15	H3	M17
E2434a-d	O15	H4	M17
E2435a-d	O15	H5	M17
E2436a-d	O15	H6	M17
E2437a-d	O15	H7	M17

Example	O Group	H Group	M Group
E2438a-d	O15	H8	M17
E2439a-d	O15	H9	M17
E2440a-d	O16	H1	M17
E2441a-d	O16	H2	M17
E2442a-d	O16	H3	M17
E2443a-d	O16	H4	M17
E2444a-d	O16	H5	M17
E2445a-d	O16	H6	M17
E2446a-d	O16	H7	M17
E2447a-d	O16	H8	M17
E2448a-d	O16	H9	M17
E2449a-d	O1	H1	M18
E2450a-d	O1	H2	M18
E2451a-d	O1	H3	M18
E2452a-d	O1	H4	M18
E2453a-d	O1	H5	M18
E2454a-d	O1	H6	M18
E2455a-d	O1	H7	M18
E2456a-d	O1	H8	M18
E2457a-d	O1	H9	M18
E2458a-d	O2	H1	M18
E2459a-d	O2	H2	M18
E2460a-d	O2	H3	M18
E2461a-d	O2	H4	M18
E2462a-d	O2	H5	M18
E2463a-d	O2	H6	M18
E2464a-d	O2	H7	M18
E2465a-d	O2	H8	M18
E2466a-d	O2	H9	M18
E2467a-d	O3	H1	M18
E2468a-d	O3	H2	M18
E2469a-d	O3	H3	M18
E2470a-d	O3	H4	M18
E2471a-d	O3	H5	M18
E2472a-d	O3	H6	M18
E2473a-d	O3	H7	M18
E2474a-d	O3	H8	M18
E2475a-d	O3	H9	M18
E2476a-d	O4	H1	M18
E2477a-d	O4	H2	M18
E2478a-d	O4	H3	M18
E2479a-d	O4	H4	M18
E2480a-d	O4	H5	M18
E2481a-d	O4	H6	M18

Example	O Group	H Group	M Group
E2482a-d	O4	H7	M18
E2483a-d	O4	H8	M18
E2484a-d	O4	H9	M18
E2485a-d	O5	H1	M18
E2486a-d	O5	H2	M18
E2487a-d	O5	H3	M18
E2488a-d	O5	H4	M18
E2489a-d	O5	H5	M18
E2490a-d	O5	H6	M18
E2491a-d	O5	H7	M18
E2492a-d	O5	H8	M18
E2493a-d	O5	H9	M18
E2494a-d	O6	H1	M18
E2495a-d	O6	H2	M18
E2496a-d	O6	H3	M18
E2497a-d	O6	H4	M18
E2498a-d	O6	H5	M18
E2499a-d	O6	H6	M18
E2500a-d	O6	H7	M18
E2501a-d	O6	H8	M18
E2502a-d	O6	H9	M18
E2503a-d	O7	H1	M18
E2504a-d	O7	H2	M18
E2505a-d	O7	H3	M18
E2506a-d	O7	H4	M18
E2507a-d	O7	H5	M18
E2508a-d	O7	H6	M18
E2509a-d	O7	H7	M18
E2510a-d	O7	H8	M18
E2511a-d	O7	H9	M18
E2512a-d	O8	H1	M18
E2513a-d	O8	H2	M18
E2514a-d	O8	H3	M18
E2515a-d	O8	H4	M18
E2516a-d	O8	H5	M18
E2517a-d	O8	H6	M18
E2518a-d	O8	H7	M18
E2519a-d	O8	H8	M18
E2520a-d	O8	H9	M18
E2521a-d	O9	H1	M18
E2522a-d	O9	H2	M18
E2523a-d	O9	H3	M18
E2524a-d	O9	H4	M18
E2525a-d	O9	H5	M18

Example	O Group	H Group	M Group
E2526a-d	O9	H6	M18
E2527a-d	O9	H7	M18
E2528a-d	O9	H8	M18
E2529a-d	O9	H9	M18
E2530a-d	O10	H1	M18
E2531a-d	O10	H2	M18
E2532a-d	O10	H3	M18
E2533a-d	O10	H4	M18
E2534a-d	O10	H5	M18
E2535a-d	O10	H6	M18
E2536a-d	O10	H7	M18
E2537a-d	O10	H8	M18
E2538a-d	O10	H9	M18
E2539a-d	O11	H1	M18
E2540a-d	O11	H2	M18
E2541a-d	O11	H3	M18
E2542a-d	O11	H4	M18
E2543a-d	O11	H5	M18
E2544a-d	O11	H6	M18
E2545a-d	O11	H7	M18
E2546a-d	O11	H8	M18
E2547a-d	O11	H9	M18
E2548a-d	O12	H1	M18
E2549a-d	O12	H2	M18
E2550a-d	O12	H3	M18
E2551a-d	O12	H4	M18
E2552a-d	O12	H5	M18
E2553a-d	O12	H6	M18
E2554a-d	O12	H7	M18
E2555a-d	O12	H8	M18
E2556a-d	O12	H9	M18
E2557a-d	O13	H1	M18
E2558a-d	O13	H2	M18
E2559a-d	O13	H3	M18
E2560a-d	O13	H4	M18
E2561a-d	O13	H5	M18
E2562a-d	O13	H6	M18
E2563a-d	O13	H7	M18
E2564a-d	O13	H8	M18
E2565a-d	O13	H9	M18
E2566a-d	O14	H1	M18
E2567a-d	O14	H2	M18
E2568a-d	O14	H3	M18
E2569a-d	O14	H4	M18

Example	O Group	H Group	M Group
E2570a-d	O14	H5	M18
E2571a-d	O14	H6	M18
E2572a-d	O14	H7	M18
E2573a-d	O14	H8	M18
E2574a-d	O14	H9	M18
E2575a-d	O15	H1	M18
E2576a-d	O15	H2	M18
E2577a-d	O15	H3	M18
E2578a-d	O15	H4	M18
E2579a-d	O15	H5	M18
E2580a-d	O15	H6	M18
E2581a-d	O15	H7	M18
E2582a-d	O15	H8	M18
E2583a-d	O15	H9	M18
E2584a-d	O16	H1	M18
E2585a-d	O16	H2	M18
E2586a-d	O16	H3	M18
E2587a-d	O16	H4	M18
E2588a-d	O16	H5	M18
E2589a-d	O16	H6	M18
E2590a-d	O16	H7	M18
E2591a-d	O16	H8	M18
E2592a-d	O16	H9	M18
E2593a-d	O1	H1	M19
E2594a-d	O1	H2	M19
E2595a-d	O1	H3	M19
E2596a-d	O1	H4	M19
E2597a-d	O1	H5	M19
E2598a-d	O1	H6	M19
E2599a-d	O1	H7	M19
E2600a-d	O1	H8	M19
E2601a-d	O1	H9	M19
E2602a-d	O2	H1	M19
E2603a-d	O2	H2	M19
E2604a-d	O2	H3	M19
E2605a-d	O2	H4	M19
E2606a-d	O2	H5	M19
E2607a-d	O2	H6	M19
E2608a-d	O2	H7	M19
E2609a-d	O2	H8	M19
E2610a-d	O2	H9	M19
E2611a-d	O3	H1	M19
E2612a-d	O3	H2	M19
E2613a-d	O3	H3	M19

Example	O Group	H Group	M Group
E2614a-d	O3	H4	M19
E2615a-d	O3	H5	M19
E2616a-d	O3	H6	M19
E2617a-d	O3	H7	M19
E2618a-d	O3	H8	M19
E2619a-d	O3	H9	M19
E2620a-d	O4	H1	M19
E2621a-d	O4	H2	M19
E2622a-d	O4	H3	M19
E2623a-d	O4	H4	M19
E2624a-d	O4	H5	M19
E2625a-d	O4	H6	M19
E2626a-d	O4	H7	M19
E2627a-d	O4	H8	M19
E2628a-d	O4	H9	M19
E2629a-d	O5	H1	M19
E2630a-d	O5	H2	M19
E2631a-d	O5	H3	M19
E2632a-d	O5	H4	M19
E2633a-d	O5	H5	M19
E2634a-d	O5	H6	M19
E2635a-d	O5	H7	M19
E2636a-d	O5	H8	M19
E2637a-d	O5	H9	M19
E2638a-d	O6	H1	M19
E2639a-d	O6	H2	M19
E2640a-d	O6	H3	M19
E2641a-d	O6	H4	M19
E2642a-d	O6	H5	M19
E2643a-d	O6	H6	M19
E2644a-d	O6	H7	M19
E2645a-d	O6	H8	M19
E2646a-d	O6	H9	M19
E2647a-d	O7	H1	M19
E2648a-d	O7	H2	M19
E2649a-d	O7	H3	M19
E2650a-d	O7	H4	M19
E2651a-d	O7	H5	M19
E2652a-d	O7	H6	M19
E2653a-d	O7	H7	M19
E2654a-d	O7	H8	M19
E2655a-d	O7	H9	M19
E2656a-d	O8	H1	M19
E2657a-d	O8	H2	M19

Example	O Group	H Group	M Group
E2658a-d	O8	H3	M19
E2659a-d	O8	H4	M19
E2660a-d	O8	H5	M19
E2661a-d	O8	H6	M19
E2662a-d	O8	H7	M19
E2663a-d	O8	H8	M19
E2664a-d	O8	H9	M19
E2665a-d	O9	H1	M19
E2666a-d	O9	H2	M19
E2667a-d	O9	H3	M19
E2668a-d	O9	H4	M19
E2669a-d	O9	H5	M19
E2670a-d	O9	H6	M19
E2671a-d	O9	H7	M19
E2672a-d	O9	H8	M19
E2673a-d	O9	H9	M19
E2674a-d	O10	H1	M19
E2675a-d	O10	H2	M19
E2676a-d	O10	H3	M19
E2677a-d	O10	H4	M19
E2678a-d	O10	H5	M19
E2679a-d	O10	H6	M19
E2680a-d	O10	H7	M19
E2681a-d	O10	H8	M19
E2682a-d	O10	H9	M19
E2683a-d	O11	H1	M19
E2684a-d	O11	H2	M19
E2685a-d	O11	H3	M19
E2686a-d	O11	H4	M19
E2687a-d	O11	H5	M19
E2688a-d	O11	H6	M19
E2689a-d	O11	H7	M19
E2690a-d	O11	H8	M19
E2691a-d	O11	H9	M19
E2692a-d	O12	H1	M19
E2693a-d	O12	H2	M19
E2694a-d	O12	H3	M19
E2695a-d	O12	H4	M19
E2696a-d	O12	H5	M19
E2697a-d	O12	H6	M19
E2698a-d	O12	H7	M19
E2699a-d	O12	H8	M19
E2700a-d	O12	H9	M19
E2701a-d	O13	H1	M19

Example	O Group	H Group	M Group
E2702a-d	O13	H2	M19
E2703a-d	O13	H3	M19
E2704a-d	O13	H4	M19
E2705a-d	O13	H5	M19
E2706a-d	O13	H6	M19
E2707a-d	O13	H7	M19
E2708a-d	O13	H8	M19
E2709a-d	O13	H9	M19
E2710a-d	O14	H1	M19
E2711a-d	O14	H2	M19
E2712a-d	O14	H3	M19
E2713a-d	O14	H4	M19
E2714a-d	O14	H5	M19
E2715a-d	O14	H6	M19
E2716a-d	O14	H7	M19
E2717a-d	O14	H8	M19
E2718a-d	O14	H9	M19
E2719a-d	O15	H1	M19
E2720a-d	O15	H2	M19
E2721a-d	O15	H3	M19
E2722a-d	O15	H4	M19
E2723a-d	O15	H5	M19
E2724a-d	O15	H6	M19
E2725a-d	O15	H7	M19
E2726a-d	O15	H8	M19
E2727a-d	O15	H9	M19
E2728a-d	O16	H1	M19
E2729a-d	O16	H2	M19
E2730a-d	O16	H3	M19
E2731a-d	O16	H4	M19
E2732a-d	O16	H5	M19
E2733a-d	O16	H6	M19
E2734a-d	O16	H7	M19
E2735a-d	O16	H8	M19
E2736a-d	O16	H9	M19
E2737a-d	O1	H1	M20
E2738a-d	O1	H2	M20
E2739a-d	O1	H3	M20
E2740a-d	O1	H4	M20
E2741a-d	O1	H5	M20
E2742a-d	O1	H6	M20
E2743a-d	O1	H7	M20
E2744a-d	O1	H8	M20
E2745a-d	O1	H9	M20

Example	O Group	H Group	M Group
E2746a-d	O2	H1	M20
E2747a-d	O2	H2	M20
E2748a-d	O2	H3	M20
E2749a-d	O2	H4	M20
E2750a-d	O2	H5	M20
E2751a-d	O2	H6	M20
E2752a-d	O2	H7	M20
E2753a-d	O2	H8	M20
E2754a-d	O2	H9	M20
E2755a-d	O3	H1	M20
E2756a-d	O3	H2	M20
E2757a-d	O3	H3	M20
E2758a-d	O3	H4	M20
E2759a-d	O3	H5	M20
E2760a-d	O3	H6	M20
E2761a-d	O3	H7	M20
E2762a-d	O3	H8	M20
E2763a-d	O3	H9	M20
E2764a-d	O4	H1	M20
E2765a-d	O4	H2	M20
E2766a-d	O4	H3	M20
E2767a-d	O4	H4	M20
E2768a-d	O4	H5	M20
E2769a-d	O4	H6	M20
E2770a-d	O4	H7	M20
E2771a-d	O4	H8	M20
E2772a-d	O4	H9	M20
E2773a-d	O5	H1	M20
E2774a-d	O5	H2	M20
E2775a-d	O5	H3	M20
E2776a-d	O5	H4	M20
E2777a-d	O5	H5	M20
E2778a-d	O5	H6	M20
E2779a-d	O5	H7	M20
E2780a-d	O5	H8	M20
E2781a-d	O5	H9	M20
E2782a-d	O6	H1	M20
E2783a-d	O6	H2	M20
E2784a-d	O6	H3	M20
E2785a-d	O6	H4	M20
E2786a-d	O6	H5	M20
E2787a-d	O6	H6	M20
E2788a-d	O6	H7	M20
E2789a-d	O6	H8	M20

Example	O Group	H Group	M Group
E2790a-d	O6	H9	M20
E2791a-d	O7	H1	M20
E2792a-d	O7	H2	M20
E2793a-d	O7	H3	M20
E2794a-d	O7	H4	M20
E2795a-d	O7	H5	M20
E2796a-d	O7	H6	M20
E2797a-d	O7	H7	M20
E2798a-d	O7	H8	M20
E2799a-d	O7	H9	M20
E2800a-d	O8	H1	M20
E2801a-d	O8	H2	M20
E2802a-d	O8	H3	M20
E2803a-d	O8	H4	M20
E2804a-d	O8	H5	M20
E2805a-d	O8	H6	M20
E2806a-d	O8	H7	M20
E2807a-d	O8	H8	M20
E2808a-d	O8	H9	M20
E2809a-d	O9	H1	M20
E2810a-d	O9	H2	M20
E2811a-d	O9	H3	M20
E2812a-d	O9	H4	M20
E2813a-d	O9	H5	M20
E2814a-d	O9	H6	M20
E2815a-d	O9	H7	M20
E2816a-d	O9	H8	M20
E2817a-d	O9	H9	M20
E2818a-d	O10	H1	M20
E2819a-d	O10	H2	M20
E2820a-d	O10	H3	M20
E2821a-d	O10	H4	M20
E2822a-d	O10	H5	M20
E2823a-d	O10	H6	M20
E2824a-d	O10	H7	M20
E2825a-d	O10	H8	M20
E2826a-d	O10	H9	M20
E2827a-d	O11	H1	M20
E2828a-d	O11	H2	M20
E2829a-d	O11	H3	M20
E2830a-d	O11	H4	M20
E2831a-d	O11	H5	M20
E2832a-d	O11	H6	M20
E2833a-d	O11	H7	M20

Example	O Group	H Group	M Group
E2834a-d	O11	H8	M20
E2835a-d	O11	H9	M20
E2836a-d	O12	H1	M20
E2837a-d	O12	H2	M20
E2838a-d	O12	H3	M20
E2839a-d	O12	H4	M20
E2840a-d	O12	H5	M20
E2841a-d	O12	H6	M20
E2842a-d	O12	H7	M20
E2843a-d	O12	H8	M20
E2844a-d	O12	H9	M20
E2845a-d	O13	H1	M20
E2846a-d	O13	H2	M20
E2847a-d	O13	H3	M20
E2848a-d	O13	H4	M20
E2849a-d	O13	H5	M20
E2850a-d	O13	H6	M20
E2851a-d	O13	H7	M20
E2852a-d	O13	H8	M20
E2853a-d	O13	H9	M20
E2854a-d	O14	H1	M20
E2855a-d	O14	H2	M20
E2856a-d	O14	H3	M20
E2857a-d	O14	H4	M20
E2858a-d	O14	H5	M20
E2859a-d	O14	H6	M20
E2860a-d	O14	H7	M20
E2861a-d	O14	H8	M20
E2862a-d	O14	H9	M20
E2863a-d	O15	H1	M20
E2864a-d	O15	H2	M20
E2865a-d	O15	H3	M20
E2866a-d	O15	H4	M20
E2867a-d	O15	H5	M20
E2868a-d	O15	H6	M20
E2869a-d	O15	H7	M20
E2870a-d	O15	H8	M20
E2871a-d	O15	H9	M20
E2872a-d	O16	H1	M20
E2873a-d	O16	H2	M20
E2874a-d	O16	H3	M20
E2875a-d	O16	H4	M20
E2876a-d	O16	H5	M20
E2877a-d	O16	H6	M20

Example	O Group	H Group	M Group
E2878a-d	O16	H7	M20
E2879a-d	O16	H8	M20
E2880a-d	O16	H9	M20
E2881a-d	O1	H1	M21
E2882a-d	O1	H2	M21
E2883a-d	O1	H3	M21
E2884a-d	O1	H4	M21
E2885a-d	O1	H5	M21
E2886a-d	O1	H6	M21
E2887a-d	O1	H7	M21
E2888a-d	O1	H8	M21
E2889a-d	O1	H9	M21
E2890a-d	O2	H1	M21
E2891a-d	O2	H2	M21
E2892a-d	O2	H3	M21
E2893a-d	O2	H4	M21
E2894a-d	O2	H5	M21
E2895a-d	O2	H6	M21
E2896a-d	O2	H7	M21
E2897a-d	O2	H8	M21
E2898a-d	O2	H9	M21
E2899a-d	O3	H1	M21
E2900a-d	O3	H2	M21
E2901a-d	O3	H3	M21
E2902a-d	O3	H4	M21
E2903a-d	O3	H5	M21
E2904a-d	O3	H6	M21
E2905a-d	O3	H7	M21
E2906a-d	O3	H8	M21
E2907a-d	O3	H9	M21
E2908a-d	O4	H1	M21
E2909a-d	O4	H2	M21
E2910a-d	O4	H3	M21
E2911a-d	O4	H4	M21
E2912a-d	O4	H5	M21
E2913a-d	O4	H6	M21
E2914a-d	O4	H7	M21
E2915a-d	O4	H8	M21
E2916a-d	O4	H9	M21
E2917a-d	O5	H1	M21
E2918a-d	O5	H2	M21
E2919a-d	O5	H3	M21
E2920a-d	O5	H4	M21
E2921a-d	O5	H5	M21

Example	O Group	H Group	M Group
E2922a-d	O5	H6	M21
E2923a-d	O5	H7	M21
E2924a-d	O5	H8	M21
E2925a-d	O5	H9	M21
E2926a-d	O6	H1	M21
E2927a-d	O6	H2	M21
E2928a-d	O6	H3	M21
E2929a-d	O6	H4	M21
E2930a-d	O6	H5	M21
E2931a-d	O6	H6	M21
E2932a-d	O6	H7	M21
E2933a-d	O6	H8	M21
E2934a-d	O6	H9	M21
E2935a-d	O7	H1	M21
E2936a-d	O7	H2	M21
E2937a-d	O7	H3	M21
E2938a-d	O7	H4	M21
E2939a-d	O7	H5	M21
E2940a-d	O7	H6	M21
E2941a-d	O7	H7	M21
E2942a-d	O7	H8	M21
E2943a-d	O7	H9	M21
E2944a-d	O8	H1	M21
E2945a-d	O8	H2	M21
E2946a-d	O8	H3	M21
E2947a-d	O8	H4	M21
E2948a-d	O8	H5	M21
E2949a-d	O8	H6	M21
E2950a-d	O8	H7	M21
E2951a-d	O8	H8	M21
E2952a-d	O8	H9	M21
E2953a-d	O9	H1	M21
E2954a-d	O9	H2	M21
E2955a-d	O9	H3	M21
E2956a-d	O9	H4	M21
E2957a-d	O9	H5	M21
E2958a-d	O9	H6	M21
E2959a-d	O9	H7	M21
E2960a-d	O9	H8	M21
E2961a-d	O9	H9	M21
E2962a-d	O10	H1	M21
E2963a-d	O10	H2	M21
E2964a-d	O10	H3	M21
E2965a-d	O10	H4	M21

Example	O Group	H Group	M Group
E2966a-d	O10	H5	M21
E2967a-d	O10	H6	M21
E2968a-d	O10	H7	M21
E2969a-d	O10	H8	M21
E2970a-d	O10	H9	M21
E2971a-d	O11	H1	M21
E2972a-d	O11	H2	M21
E2973a-d	O11	H3	M21
E2974a-d	O11	H4	M21
E2975a-d	O11	H5	M21
E2976a-d	O11	H6	M21
E2977a-d	O11	H7	M21
E2978a-d	O11	H8	M21
E2979a-d	O11	H9	M21
E2980a-d	O12	H1	M21
E2981a-d	O12	H2	M21
E2982a-d	O12	H3	M21
E2983a-d	O12	H4	M21
E2984a-d	O12	H5	M21
E2985a-d	O12	H6	M21
E2986a-d	O12	H7	M21
E2987a-d	O12	H8	M21
E2988a-d	O12	H9	M21
E2989a-d	O13	H1	M21
E2990a-d	O13	H2	M21
E2991a-d	O13	H3	M21
E2992a-d	O13	H4	M21
E2993a-d	O13	H5	M21
E2994a-d	O13	H6	M21
E2995a-d	O13	H7	M21
E2996a-d	O13	H8	M21
E2997a-d	O13	H9	M21
E2998a-d	O14	H1	M21
E2999a-d	O14	H2	M21
E3000a-d	O14	H3	M21
E3001a-d	O14	H4	M21
E3002a-d	O14	H5	M21
E3003a-d	O14	H6	M21
E3004a-d	O14	H7	M21
E3005a-d	O14	H8	M21
E3006a-d	O14	H9	M21
E3007a-d	O15	H1	M21
E3008a-d	O15	H2	M21
E3009a-d	O15	H3	M21

Example	O Group	H Group	M Group
E3010a-d	O15	H4	M21
E3011a-d	O15	H5	M21
E3012a-d	O15	H6	M21
E3013a-d	O15	H7	M21
E3014a-d	O15	H8	M21
E3015a-d	O15	H9	M21
E3016a-d	O16	H1	M21
E3017a-d	O16	H2	M21
E3018a-d	O16	H3	M21
E3019a-d	O16	H4	M21
E3020a-d	O16	H5	M21
E3021a-d	O16	H6	M21
E3022a-d	O16	H7	M21
E3023a-d	O16	H8	M21
E3024a-d	O16	H9	M21
E3025a-d	O1	H1	M22
E3026a-d	O1	H2	M22
E3027a-d	O1	H3	M22
E3028a-d	O1	H4	M22
E3029a-d	O1	H5	M22
E3030a-d	O1	H6	M22
E3031a-d	O1	H7	M22
E3032a-d	O1	H8	M22
E3033a-d	O1	H9	M22
E3034a-d	O2	H1	M22
E3035a-d	O2	H2	M22
E3036a-d	O2	H3	M22
E3037a-d	O2	H4	M22
E3038a-d	O2	H5	M22
E3039a-d	O2	H6	M22
E3040a-d	O2	H7	M22
E3041a-d	O2	H8	M22
E3042a-d	O2	H9	M22
E3043a-d	O3	H1	M22
E3044a-d	O3	H2	M22
E3045a-d	O3	H3	M22
E3046a-d	O3	H4	M22
E3047a-d	O3	H5	M22
E3048a-d	O3	H6	M22
E3049a-d	O3	H7	M22
E3050a-d	O3	H8	M22
E3051a-d	O3	H9	M22
E3052a-d	O4	H1	M22
E3053a-d	O4	H2	M22

Example	O Group	H Group	M Group
E3054a-d	O4	H3	M22
E3055a-d	O4	H4	M22
E3056a-d	O4	H5	M22
E3057a-d	O4	H6	M22
E3058a-d	O4	H7	M22
E3059a-d	O4	H8	M22
E3060a-d	O4	H9	M22
E3061a-d	O5	H1	M22
E3062a-d	O5	H2	M22
E3063a-d	O5	H3	M22
E3064a-d	O5	H4	M22
E3065a-d	O5	H5	M22
E3066a-d	O5	H6	M22
E3067a-d	O5	H7	M22
E3068a-d	O5	H8	M22
E3069a-d	O5	H9	M22
E3070a-d	O6	H1	M22
E3071a-d	O6	H2	M22
E3072a-d	O6	H3	M22
E3073a-d	O6	H4	M22
E3074a-d	O6	H5	M22
E3075a-d	O6	H6	M22
E3076a-d	O6	H7	M22
E3077a-d	O6	H8	M22
E3078a-d	O6	H9	M22
E3079a-d	O7	H1	M22
E3080a-d	O7	H2	M22
E3081a-d	O7	H3	M22
E3082a-d	O7	H4	M22
E3083a-d	O7	H5	M22
E3084a-d	O7	H6	M22
E3085a-d	O7	H7	M22
E3086a-d	O7	H8	M22
E3087a-d	O7	H9	M22
E3088a-d	O8	H1	M22
E3089a-d	O8	H2	M22
E3090a-d	O8	H3	M22
E3091a-d	O8	H4	M22
E3092a-d	O8	H5	M22
E3093a-d	O8	H6	M22
E3094a-d	O8	H7	M22
E3095a-d	O8	H8	M22
E3096a-d	O8	H9	M22
E3097a-d	O9	H1	M22

Example	O Group	H Group	M Group
E3098a-d	O9	H2	M22
E3099a-d	O9	H3	M22
E3100a-d	O9	H4	M22
E3101a-d	O9	H5	M22
E3102a-d	O9	H6	M22
E3103a-d	O9	H7	M22
E3104a-d	O9	H8	M22
E3105a-d	O9	H9	M22
E3106a-d	O10	H1	M22
E3107a-d	O10	H2	M22
E3108a-d	O10	H3	M22
E3109a-d	O10	H4	M22
E3110a-d	O10	H5	M22
E3111a-d	O10	H6	M22
E3112a-d	O10	H7	M22
E3113a-d	O10	H8	M22
E3114a-d	O10	H9	M22
E3115a-d	O11	H1	M22
E3116a-d	O11	H2	M22
E3117a-d	O11	H3	M22
E3118a-d	O11	H4	M22
E3119a-d	O11	H5	M22
E3120a-d	O11	H6	M22
E3121a-d	O11	H7	M22
E3122a-d	O11	H8	M22
E3123a-d	O11	H9	M22
E3124a-d	O12	H1	M22
E3125a-d	O12	H2	M22
E3126a-d	O12	H3	M22
E3127a-d	O12	H4	M22
E3128a-d	O12	H5	M22
E3129a-d	O12	H6	M22
E3130a-d	O12	H7	M22
E3131a-d	O12	H8	M22
E3132a-d	O12	H9	M22
E3133a-d	O13	H1	M22
E3134a-d	O13	H2	M22
E3135a-d	O13	H3	M22
E3136a-d	O13	H4	M22
E3137a-d	O13	H5	M22
E3138a-d	O13	H6	M22
E3139a-d	O13	H7	M22
E3140a-d	O13	H8	M22
E3141a-d	O13	H9	M22

Example	O Group	H Group	M Group
E3142a-d	O14	H1	M22
E3143a-d	O14	H2	M22
E3144a-d	O14	H3	M22
E3145a-d	O14	H4	M22
E3146a-d	O14	H5	M22
E3147a-d	O14	H6	M22
E3148a-d	O14	H7	M22
E3149a-d	O14	H8	M22
E3150a-d	O14	H9	M22
E3151a-d	O15	H1	M22
E3152a-d	O15	H2	M22
E3153a-d	O15	H3	M22
E3154a-d	O15	H4	M22
E3155a-d	O15	H5	M22
E3156a-d	O15	H6	M22
E3157a-d	O15	H7	M22
E3158a-d	O15	H8	M22
E3159a-d	O15	H9	M22
E3160a-d	O16	H1	M22
E3161a-d	O16	H2	M22
E3162a-d	O16	H3	M22
E3163a-d	O16	H4	M22
E3164a-d	O16	H5	M22
E3165a-d	O16	H6	M22
E3166a-d	O16	H7	M22
E3167a-d	O16	H8	M22
E3168a-d	O16	H9	M22

3. Synthesis of the Compounds of the Invention

In another aspect, the invention provides methods for making the compounds of the invention. The following schemes depict some exemplary chemistries available for synthesizing the compounds of the invention. It will be appreciated, however, that the desired compounds may be synthesized using other alternative chemistries known in the art.

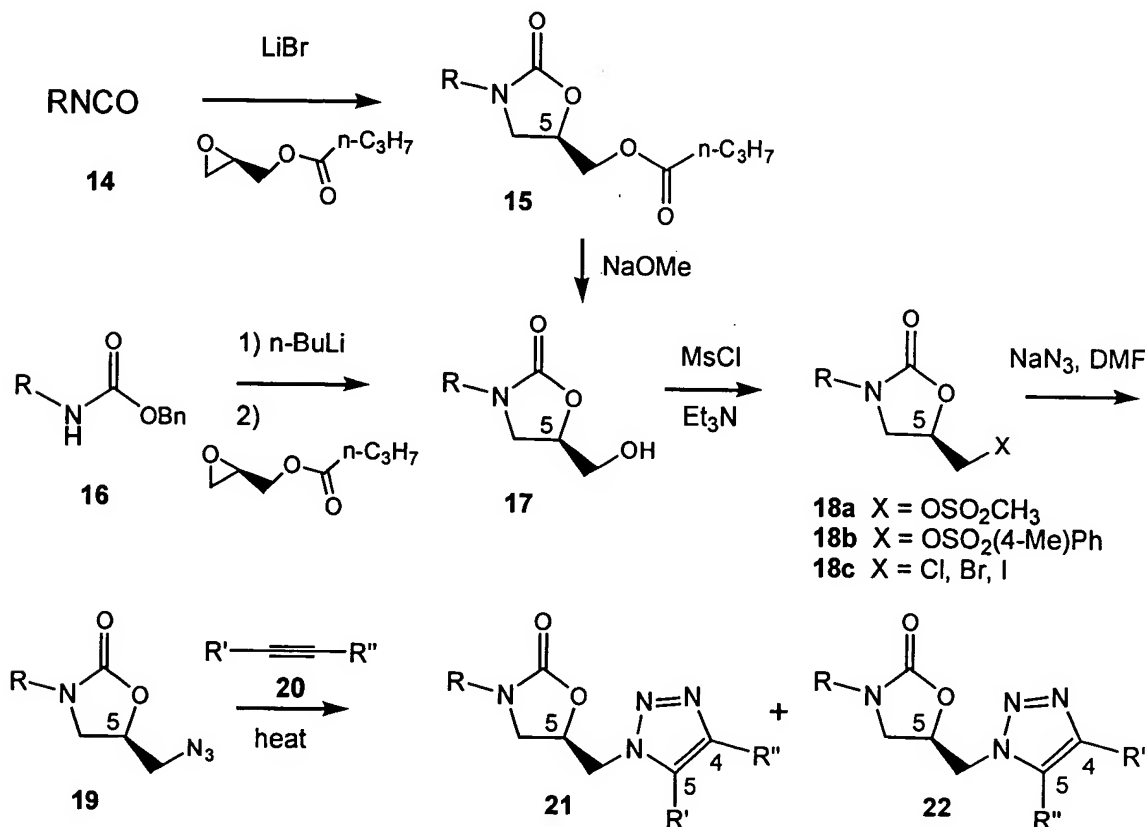
Scheme 1 illustrates the synthesis of oxazolidinones substituted at C-5 with 1,2,3-triazolylmethyl derivatives. Isocyanates **14** can react with lithium bromide and glycidyl butyrate at elevated temperature to produce oxazolidinone intermediates of type **15** (Gregory *et al.* (1989) J. MED. CHEM. 32: 1673). Hydrolysis of the resulting butyrate ester of compound **15** produces alcohol **17**. Alcohol **17** can also be synthesized from carbamates such as the benzyl carbamate **16**. The carbamate nitrogen of compound **16** then is deprotonated, and alkylated with glycidyl

butyrate to produce (after *in situ* hydrolysis of the butyl ester) hydroxymethyl derivative 17.

While the R enantiomer depicted throughout Scheme 1 generally is the most biologically useful derivative for antibacterial agents, it is contemplated that compounds derived from either the R or the S enantiomer, or any mixture of R and S enantiomers, may be useful in the practice of the invention.

Alcohols 17 can be converted to useful intermediates such as mesylates 18a (by treatment with methanesulfonyl chloride and triethylamine in an appropriate solvent) and azide 19 (by subsequent displacement of the mesylate by sodium azide in DMF). Azide 19 can also be produced from tosylate 18b (or a brosylate or nosylate), or an alkyl halide of type 18c (made from alcohol 17 via methods known to those skilled in the art). Azide 19 can be heated in the presence of substituted acetylenes 20 to produce C-5 substituted 1,2,3-triazolylmethyl oxazolidinone derivatives of type 21 and 22. It is to be understood that alternative chemical conditions could be employed by those skilled in the art to effect this transformation.

Scheme 1

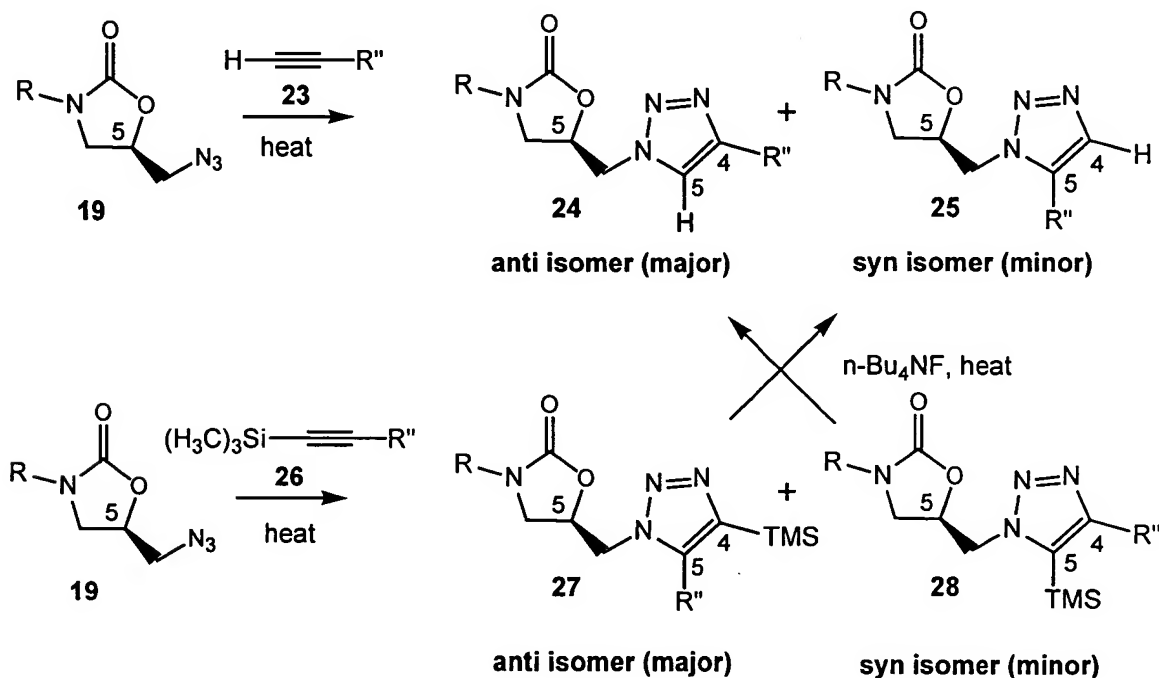


It is understood that unsymmetrical acetylene derivatives can react to produce a mixture of regioisomeric cycloaddition products, represented by **21** and **22**, and that the reaction conditions can be adjusted by processes known to those skilled in the art to produce more selectively one regioisomer or the other. For example, Scheme 2 depicts the reaction of mono-

5 substituted acetylene **23** with azide **19** to produce two regioisomeric triazoles, **24** and **25**. The major isomer is most often the anti isomer **24** since the reaction leading to this product proceeds at a faster rate. Under certain circumstances, the more sterically disfavored syn isomer is also formed, but at an appreciably diminished rate. The addition of copper(I)iodide is a useful additive for this reaction, and often leads to increased proportions of the major “anti” adduct **24**

10 (Tornoe, C.W. *et al.* (2002) J. ORG. CHEM. 67: 3057). Increased proportions of the minor isomer **25** may be produced by minor modification of the reaction scheme. Azide **19** can react with the trimethylsilyl substituted acetylene **26** to produce the anti isomer **27** and the syn isomer **28**. Desilylation with tetrabutylammonium fluoride can produce triazole **24** and **25**, with increased proportions of **25** obtainable from the more abundant precursor triazole **27**.

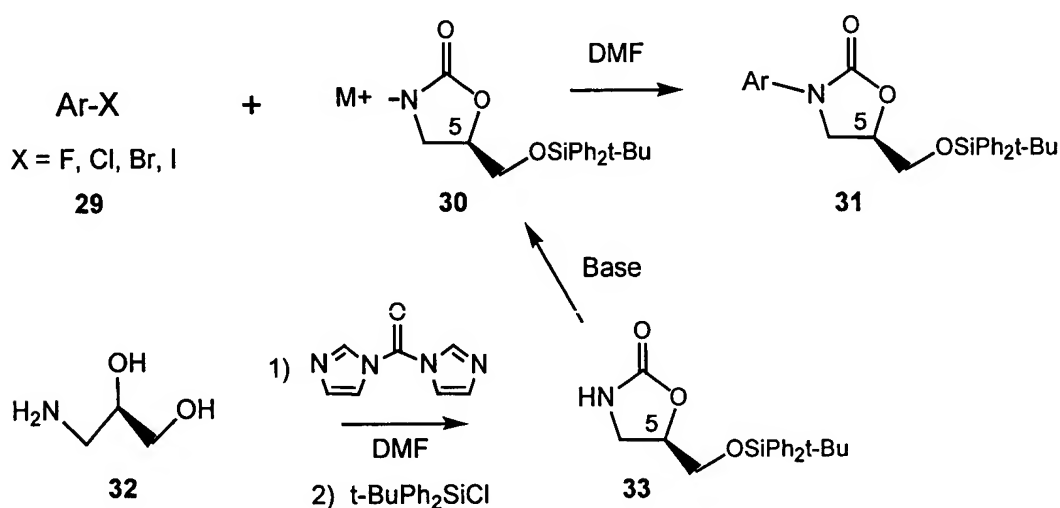
Scheme 2



An alternate approach toward the synthesis of some of the compounds of the present invention is shown in Scheme 3. Aromatic halide **29**, when activated, can react with the anion

derived from treatment of carbamate **33** with an appropriate base to produce 3-aryl substituted oxazolidinone derivatives **31** via nucleophilic aromatic substitution. Suitable bases include, for example, *n*-BuLi, LiN(Si(CH₃)₃)₂, and NaH. Carbamate **33** can be synthesized by exposure of **32** to carbonyldiimidazole in DMF, followed by *in situ* silylation of the hydroxymethyl group of the initial product with an appropriate silyl chloride. Desilylation of derivatives of type **31** produces alcohols **17** that can be converted to the targets of the present invention by the processes described within the schemes.

Scheme 3



Scheme 4a illustrates the synthesis of some alkynes of type **23** required for the synthesis of some of the compounds of the present invention. Secondary alkyl amines (or cycloalkyl amines) can be alkylated with electrophiles comprised of an alkyne connected by a variable bond or linker to a carbon bearing a leaving group, for example, a halide or sulfonate group (**35**), to produce alkynes of type **36**. The substituted alkynes can be used in cycloaddition reactions with azides to yield triazole-linked target compounds. The amino group undergoing such an alkylation can be derived from amino saccharides, for example (but not limited to), the des-methyl desosamine derivative **37**. Desosamine derivative **37** is available from the degradation of erythromycin. Alkylation of **37** with alkynes **35** produces triazole-linked sugar compounds of type **38**. The dimethyl amino group of the desosamine sugar of macrolide antibiotics can be monodemethylated to produce the corresponding secondary amine (U.S. Patent No. 3,725,385, Flynn *et al.* (1954) J. AM. CHEM. SOC. 76: 3121; Ku *et al.* (1997) BIOORG. MED. CHEM.

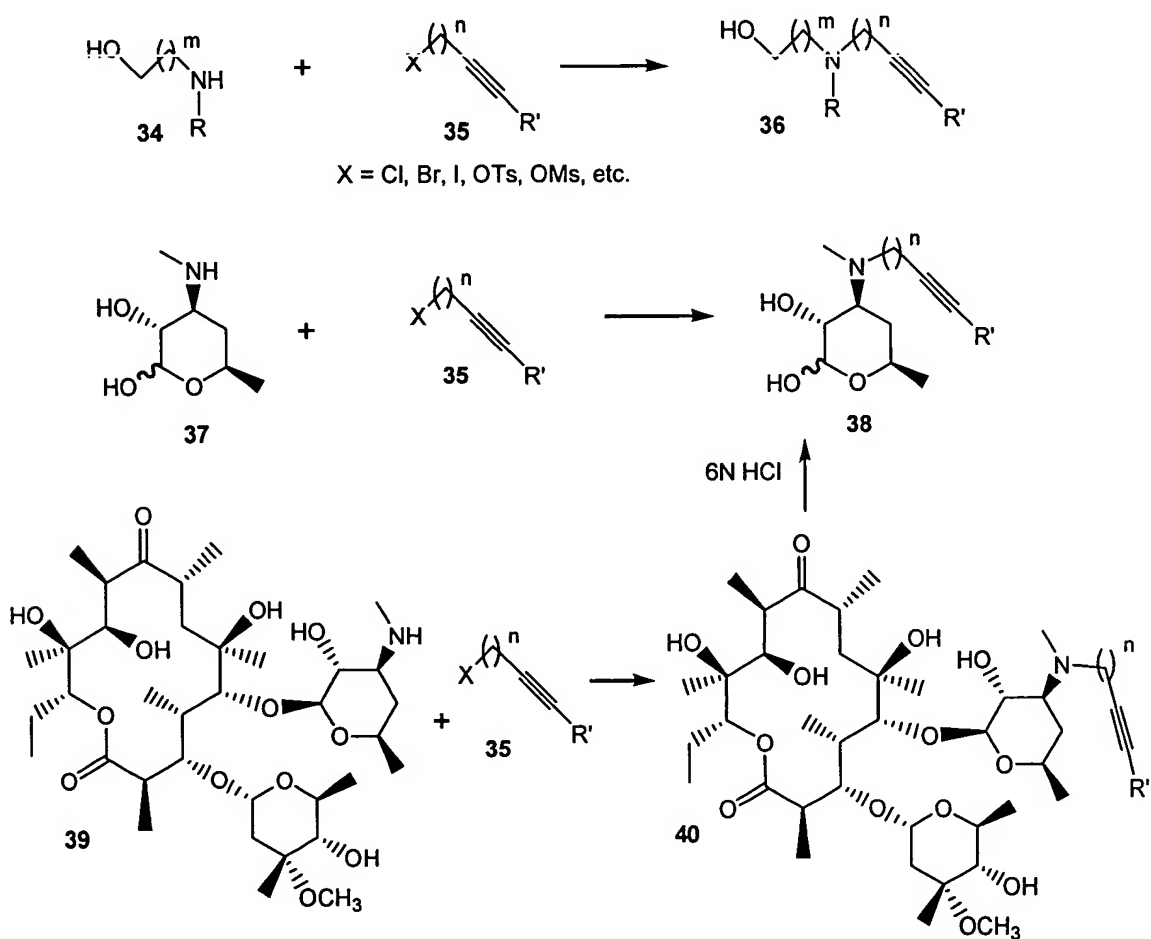
LETT. 7: 1203; Stenmark *et al.* (2000) J. ORG. CHEM. 65: 3875). For example, amine **39** (an intermediate in the synthesis of amino sugar **37**), or a suitably protected derivative of **39** such as the per-silylated compound (formed by pre-treatment with bis-trimethylsilylacetamide, hexamethyldisilazane or other agents known in the art) can be alkylated with alkynes of type **35**.

- 5 This alkylation reaction produces intermediates of type **40**, that can react with azides of type **19** to yield target compounds.

An alternative route is available for the production of desosamine derivatives **38**.

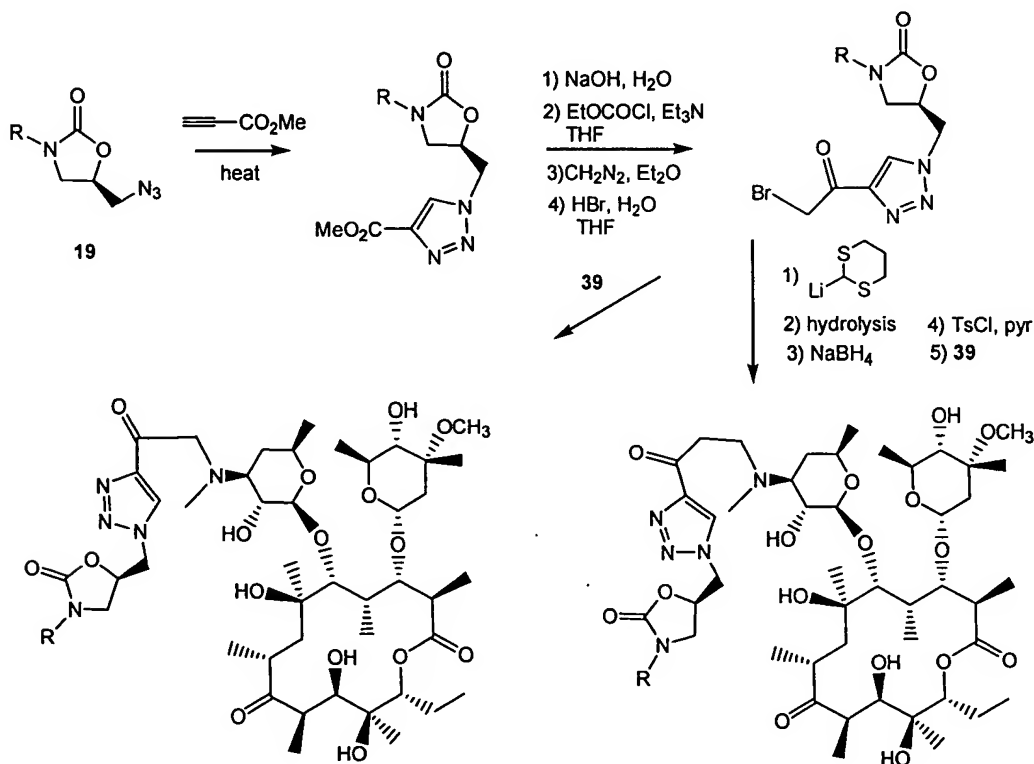
- Alkynes **40** can be hydrolyzed with strong acid to produce amines **38**. It is understood that, given appropriate reaction conditions known to those skilled in the art, any macrolide
 10 antibacterial agent (naturally occurring, semi-synthetic or synthesized) is capable of serving as starting material for the processes depicted in Scheme 4a.

Scheme 4a



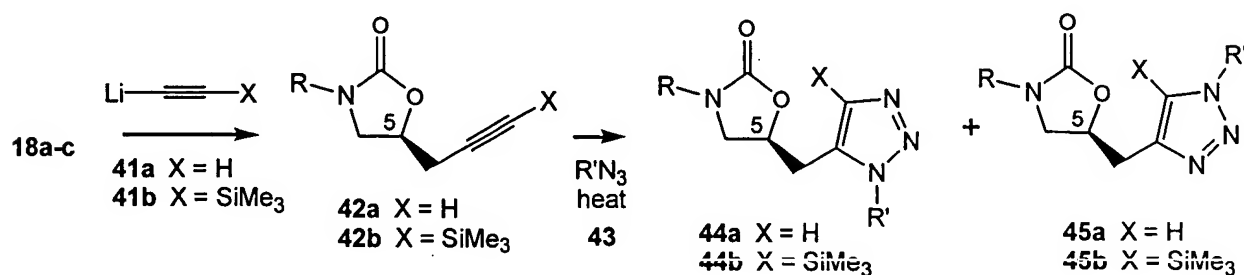
Scheme 4b illustrates the synthesis of compounds of the present invention that contain extra keto groups in the alkyl link between the 5-membered heterocyclic ring and the macrolide moiety. Azides **19** can react with propiolate esters to produce the ester-substituted products. (It is to be understood that mixtures of regioisomeric cycloadducts may form in this reaction, however, only the anti adduct is depicted in Scheme 4b.) Hydrolysis of the ester yields the acid, which can be converted using known chemistry (Ramtohul *et al.* (2000) J. ORG. CHEM. 67: 3169) to the bromoacetyl triazole. Heating this bromoacetyl derivative with **39** (or a suitably protected version of **39**) can yield products that contain a keto link with one methylene group between the ketone and the macrolide group. The bromoacetyl intermediate can be converted via lithio-dithiane chemistry, subsequent hydrolysis, and reduction to an alcohol. The tosylate (or halide) of this alcohol can be made, and this electrophile can be used to alkylate **39** to give products with two methylene groups between the ketone and the macrolide group.

15 Scheme 4b



Scheme 5 illustrates another method to synthesize regioisomeric triazole-linked derivatives of the invention. Carbon-linked triazole derivatives of type **44** and **45** can be produced by first displacing a leaving group (for example, a sulfonate or a halide) from electrophiles **18a-c**, with either lithium acetylide **41a** or lithium trimethylsilylacetylide **41b** to produce alkynes **42**. The cycloaddition reaction of alkynes **42** with appropriate azides **43** can yield regioisomeric triazoles **44** and **45**. (It will be understood that alternative chemical conditions could be employed to produce compounds **44** and **45** such as the use of copper(I)iodide instead of heat).

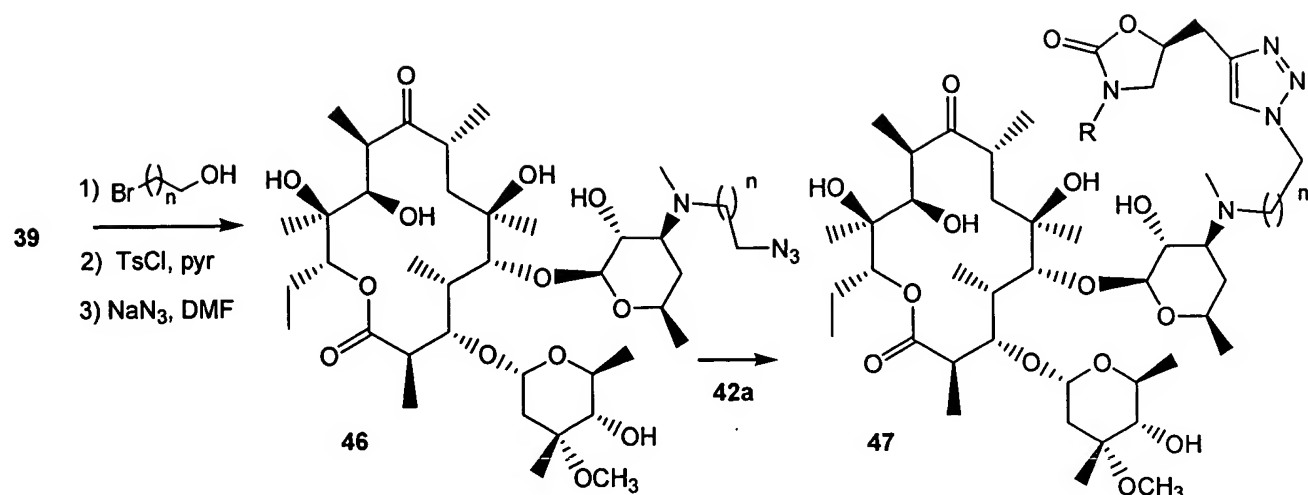
10 Scheme 5



A specific example of the utility of the chemistry expressed in Scheme 5 is shown in Scheme 6. Des-methyl erythromycin derivative **39** (or a suitably protected derivative thereof) can be alkylated with a bromoalcohol, and the alcohol function of the product converted to a leaving group such as a tosylate. The tosylate can be displaced with sodium azide to yield azide **46**. Cycloaddition of **46** and alkyne **42a** can produce final targets of type **47**. Alternative alkylsulfonates or halides can be used as the starting material for the synthesis of azide **46** (i.e., different leaving groups). Other macrolide entities can be used in place of the des-methyl erythromycin derivative **39** to produce a variety of alternative products.

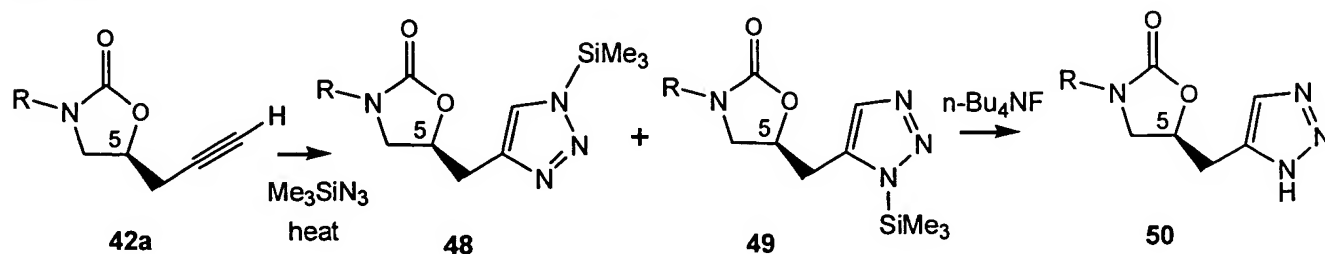
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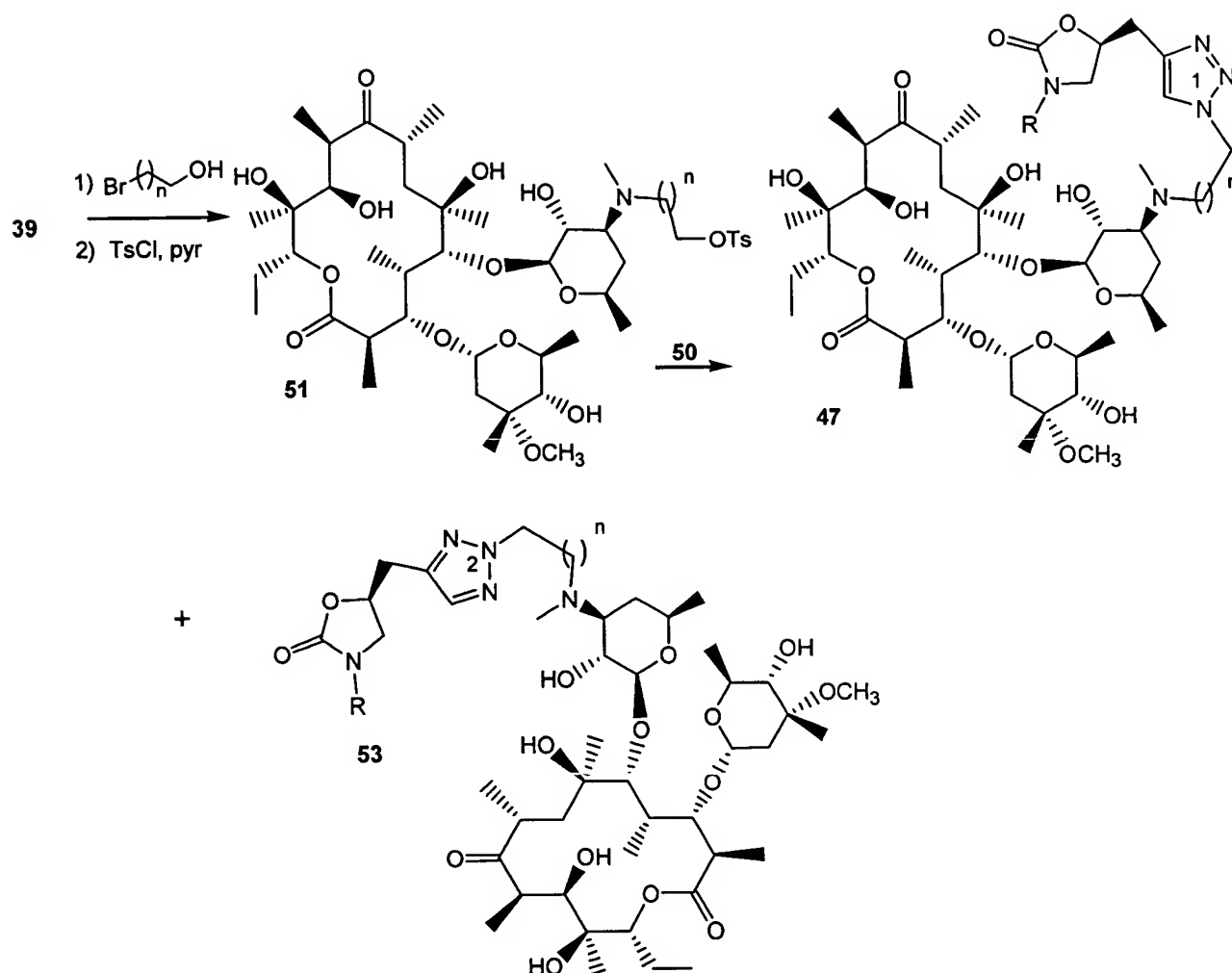
Scheme 6



Another method that can be used to synthesize carbon-linked triazole derivatives of type 47 is illustrated in Scheme 7. Alkyne 42a can react with trimethylsilylazide (or with sodium azide, ammonium chloride and copper(I)iodide, or other conditions known in the art) to produce two possible regioisomeric products, triazoles 48 and 49. Either of these (or the mixture) can be desilylated with $n\text{-Bu}_4\text{NF}$ to produce triazole 50. Des-methyl erythromycin derivative 39 (or an alternate des-methyl amino macrolide derivative) can be converted to tosylate 51 (or another sulfonate or halide electrophile), and then the electrophile can serve to alkylate triazole 50 to produce either the N-1 substituted triazole 47, or the N-2 substituted triazole 53, or a mixture of both. In the event that a mixture is produced, both compounds may be separated from one another. It is contemplated that other macrolides may be transformed by the chemistry of Scheme 7 to produce other compounds of interest.

Scheme 7

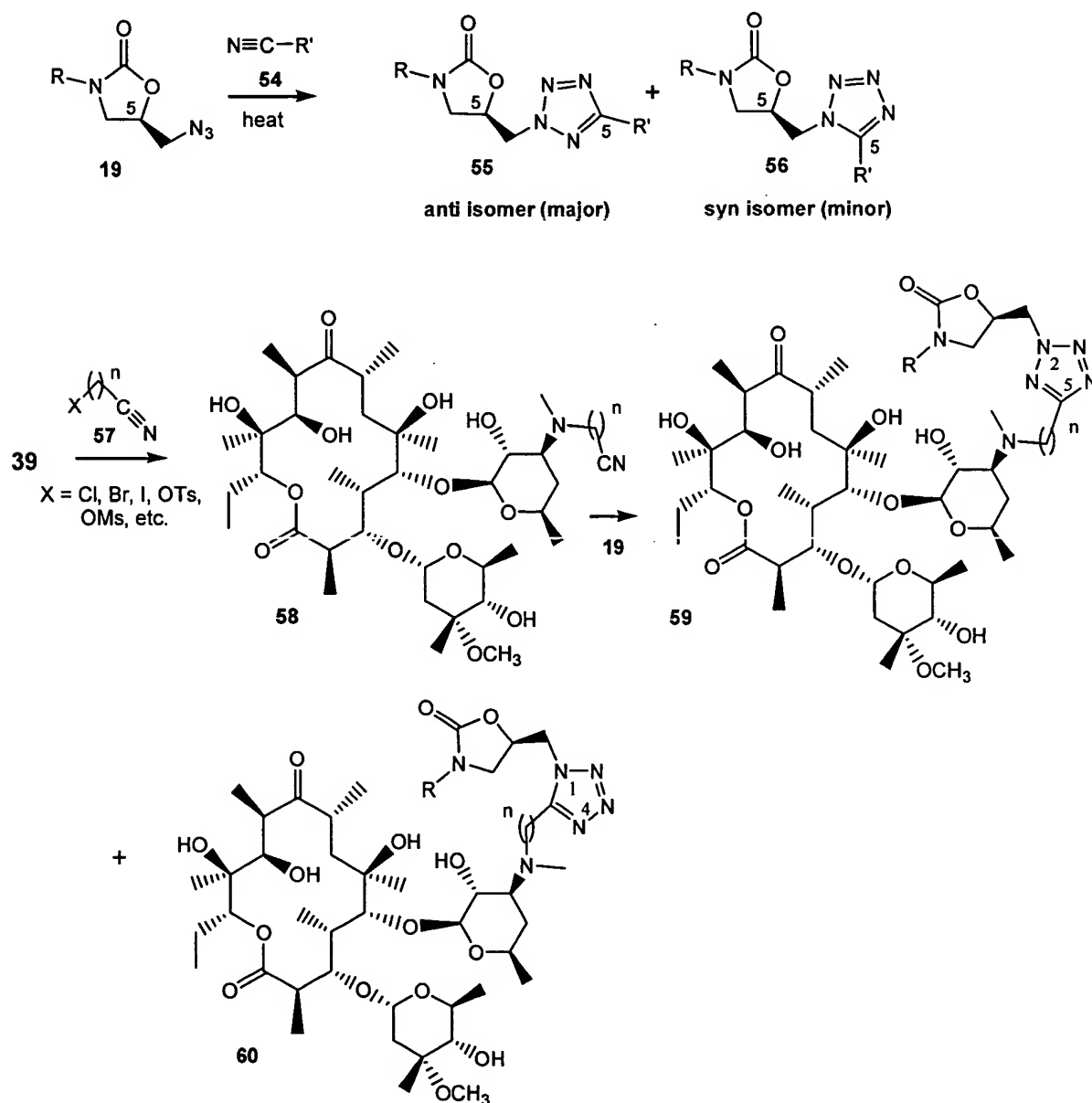




Scheme 8a illustrates the synthesis of oxazolidinones substituted at C-5 with tetrazolylmethyl derivatives. Azides of type **19** can react with nitriles **54** to produce tetrazoles of type **55** and **56**. In a similar fashion to the chemistry described in Scheme 1, this reaction can yield regioisomeric cycloadducts, where the anti isomer often predominates. As an example, des-methyl erythromycin **39** can be alkylated with ω -halo or ω -sulfonate nitriles to yield nitriles **57**. These derivatives can react with azides of type **19** to produce target tetrazoles of type **59** and **60**. It is to be understood that the R' group of nitriles **54** may contain the macrolide moiety, or suitable substituted alkyl groups containing an alcohol or protected alcohol that could be converted to a leaving group prior to a final alkylation step with a macrolide amine. Thus, the tetrazoles **55** and **56** could be produced that have as their R' groups alkyl chains bearing a hydroxy group that can be converted into a sulfonate or halide leaving group prior to alkylation with amines similar to **39** to afford products of type **59** and **60**. The hydroxy group may be

unmasked from a protected hydroxyl group in the compounds **55** and **56** prior to further conversions as mentioned above to afford targets of type **59** and **60**.

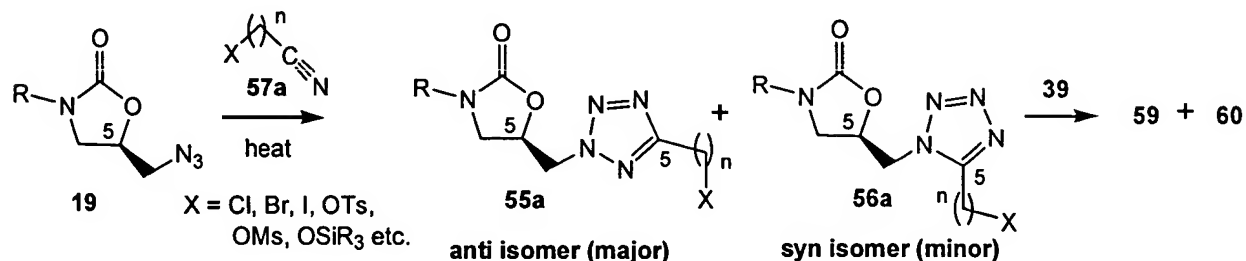
Scheme 8a



Scheme 8b depicts another strategy to synthesize tetrazoles of type **59** and **60**. Azides **19** could undergo cycloaddition to functionalized nitriles of type **57a** to afford tetrazole intermediates **55a** and **56a**. If **55a** and **56a** contain an appropriate electrophilic group such as a halide or sulfonate, it can react directly with macrocycle amines of type **39** (or a suitably protected derivative thereof) to yield targets of type **59** and **60**. Alternatively, silyloxy-substituted nitriles

57a could be used during the cycloaddition reaction to afford intermediates of type **55a** and **56a** where X is a silyloxy group. The silylether protecting group could then be removed from **55a** and **56a**, and the resultant alcohol converted to an appropriate electrophile (such as a halide or sulfonate) that would then be suitable for alkylation of macrolide amines of type **39** to give the desired targets.

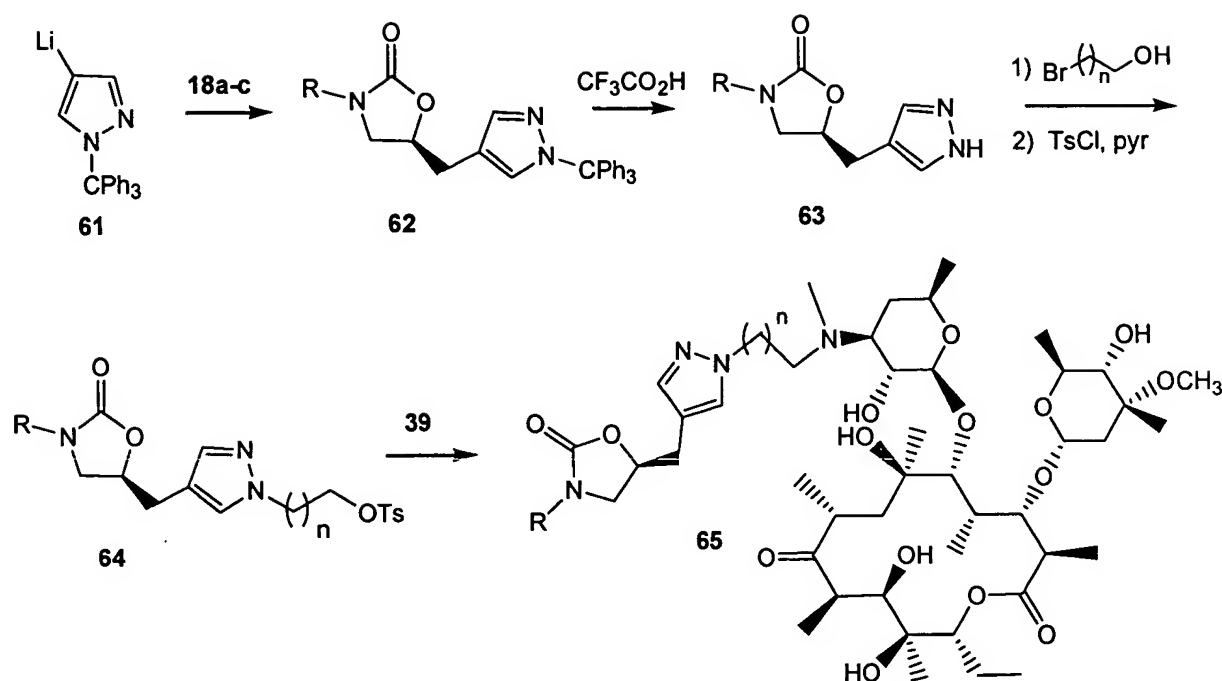
Scheme 8b



It will be understood that if the alkyl group bearing substituent X in **55a** and **56a** contains a hydroxyl group, the group could be oxidized to an aldehyde by methods well known to those skilled in the art. Such aldehydes could be used to produce targets of type **59** and **60** via the use of reductive amination conditions employed on these aldehydes and macrolide amines similar to amine **39** (or suitably protected variants thereof).

Scheme 9 illustrates one method of synthesizing pyrazole derivatives of the present invention. Known trityl-protected organolithium derivative **61** (Elguero *et al.* (1997) SYNTHESIS 563) can be alkylated with electrophiles of type **18a-c** to produce pyrazoles of type **62**. Cleavage of the trityl group can be accomplished using a variety of acidic reagents, for example, trifluoroacetic acid (TFA), to produce pyrazole **63**. Alkylation of **63** with a bromoalcohol of appropriate length, followed by tosylation (or alternate sulfonation or halide formation) can produce electrophiles **64**. Alkylation of **39** with **64** produces targets of type **65**. The lithium anions derived from heterocycles such as **61** may optionally be converted to copper (or other metallic) derivatives to facilitate their displacement reactions with sulfonates and halides. These anions may also be allowed to react with suitably protected macrolides, such as the per-silylated derivative of **51**.

Scheme 9



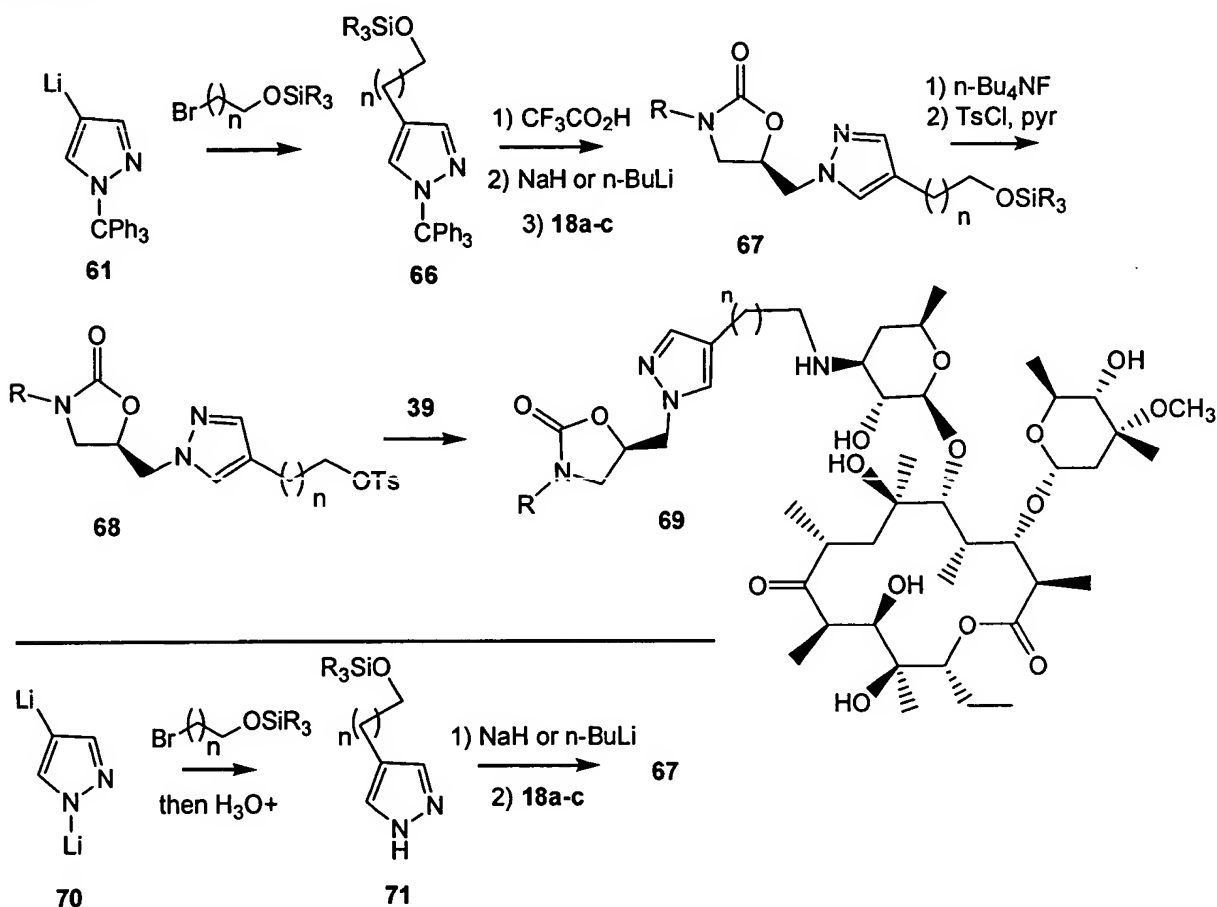
Scheme 10 depicts another method of synthesizing pyrazoles of the present invention. Anions **61** can be alkylated with a bifunctional linker of variable length such as an alkyl halide containing a silyloxy derivative. Alternatively an α,ω dihaloalkyl derivative can be used as the alkylating agent, or a mixed halo-sulfonate can be employed for this purpose. The resulting substituted pyrazoles **66** can be converted to the free pyrazoles by TFA cleavage of the triphenylmethyl protecting group. The free pyrazoles can undergo direct alkylation with electrophiles **18a-c** in a suitable solvent, for example, dimethylformamide, or can be first converted via deprotonation with a suitable base, for example, sodium hydride or n-butyllithium, to the corresponding anion, if a more reactive nucleophile is required. The resultant pyrazole derivatives **67** can be desilylated and converted to tosylates **68** (if a sulfonate strategy is employed), which can serve as electrophiles for subsequent reaction with macrolide aminosaccharides, for example, amine **39**, to produce the resultant target **69**.

Another approach to intermediates of type **67** can start with alkylation of the known dianion **70** (Hahn *et al.* (1991) J. HETEROCYCLIC CHEMISTRY 28: 1189) with an appropriate bifunctional linker to produce compounds related to pyrazole **71**, which can subsequently be alkylated (with or without prior deprotonation) with electrophiles **18a-c** to produce intermediates **67**. The $n = 1$ derivatives in this series can be synthesized by trapment of compound **61** with DMF to produce the corresponding aldehyde, and then reduction to the

alcohol. Alternatively, methoxymethyl (MOM) chloride or bromide can serve as the alkylating reagent for **61**, and hydrolysis of the trityl and MOM groups of the product would yield 4-hydroxymethyl-1,2-pyrazole. The dianion of this pyrazole can be alkylated on nitrogen to produce an alcohol that serves as the precursor for a $n = 1$ tosylate (or other leaving group).

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Scheme 10

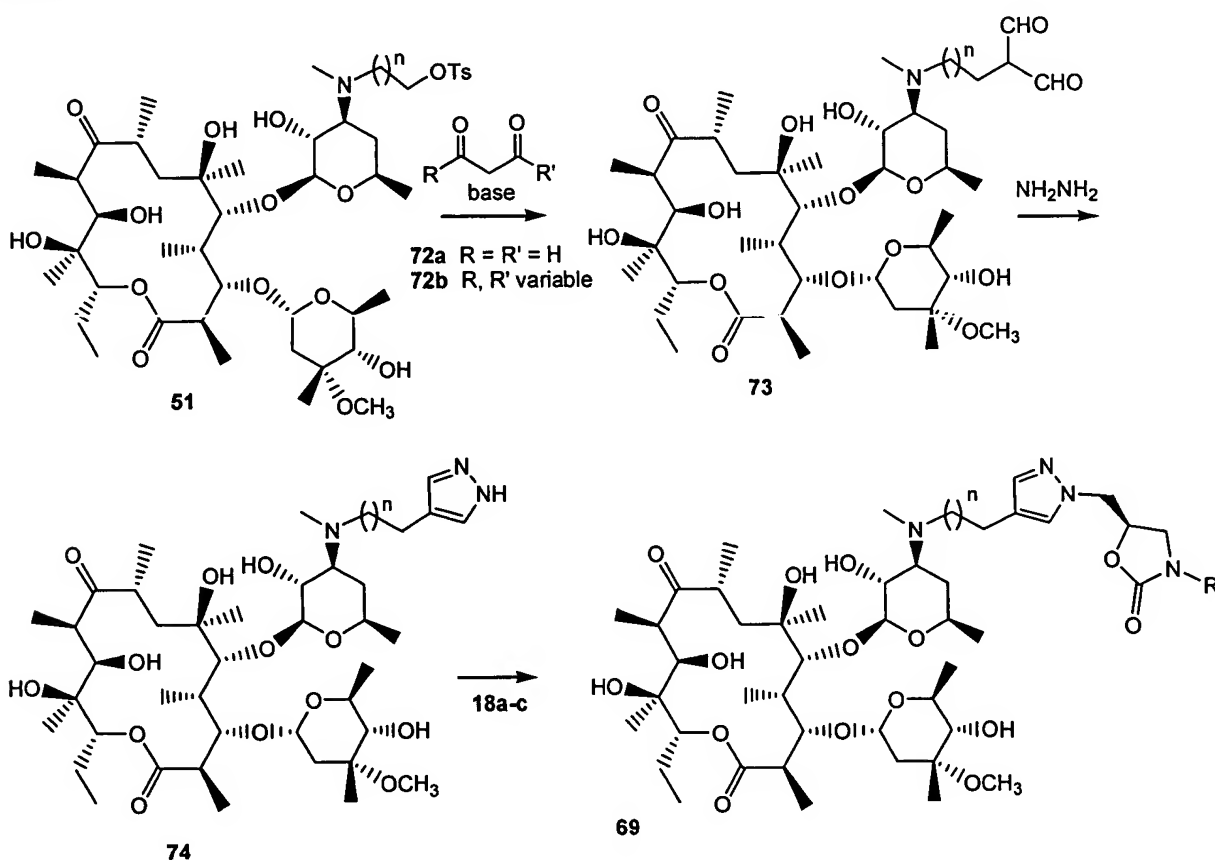


Scheme 11 shows an alternate approach for synthesizing pyrazole derivatives of type **69**.

- 10 Alkylation of the anion of a β -dicarbonyl system with appropriate electrophiles similar to tosylate **51** can yield (in the specific example of β -dicarbonyl derivative **72a**) products of type **73**. Treatment of these intermediates with hydrazine can produce pyrazoles of type **74**. Direct alkylation of **74** with electrophiles **18a-c** can proceed to produce targets **69**. Alternatively, the hydroxyl residues of **74** (and other sensitive functional groups of other macrolide derivatives
- 15 such as intermediates **39** and **51**) can be protected with suitable protecting groups (such as those

highlighted in Greene, T.W. and Wuts, P.G.M. *supra*), and the hydrogen atom on the nitrogen atom of the pyrazole derivative deprotonated with a suitable base, for example, sodium hydride or n-butyllithium. The resulting anion can then be alkylated with electrophiles **18a-c**, and the resulting product deprotected to produce targets **69**. The use of protecting groups well known to those skilled in the art for the macrolide portions of these intermediates may be required for many of the subsequent reactions shown in the schemes below that involve heteroaryl anion alkylations.

Scheme 11

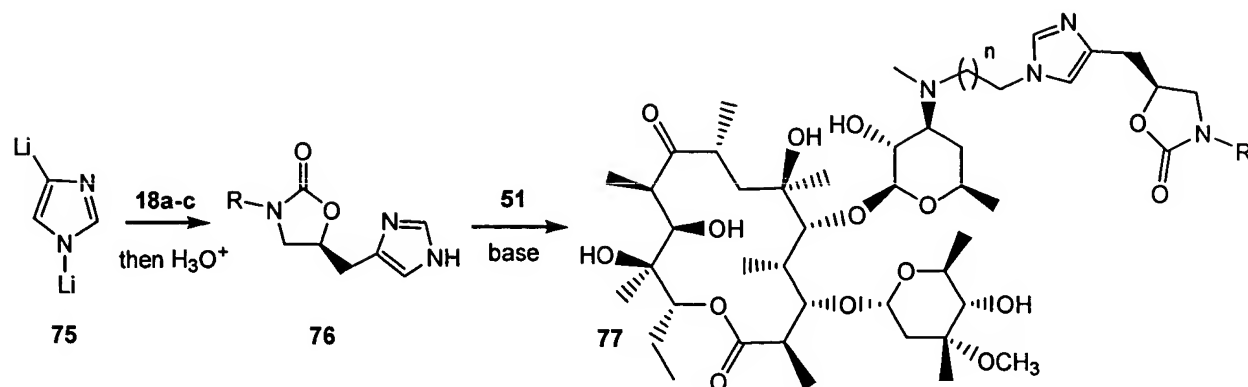


Scheme 12 exemplifies a synthesis of imidazoles of the present invention. The known dianion **75** (Katritzky *et al.* (1989) J. CHEM. SOC. PERKIN TRANS. 1: 1139) can react with electrophiles **18a-c** to produce after protic work-up imidazoles of type **76**. Direct alkylation of **76** by heating with electrophiles related to **51** in an appropriate organic solvent can yield 1,4-disubstituted imidazoles **77**. Alternatively, the imidazole anion formed via deprotonation of the

imidazole hydrogen atom of **76** with a suitable base and then alkylation with **51** can also produce **77**.

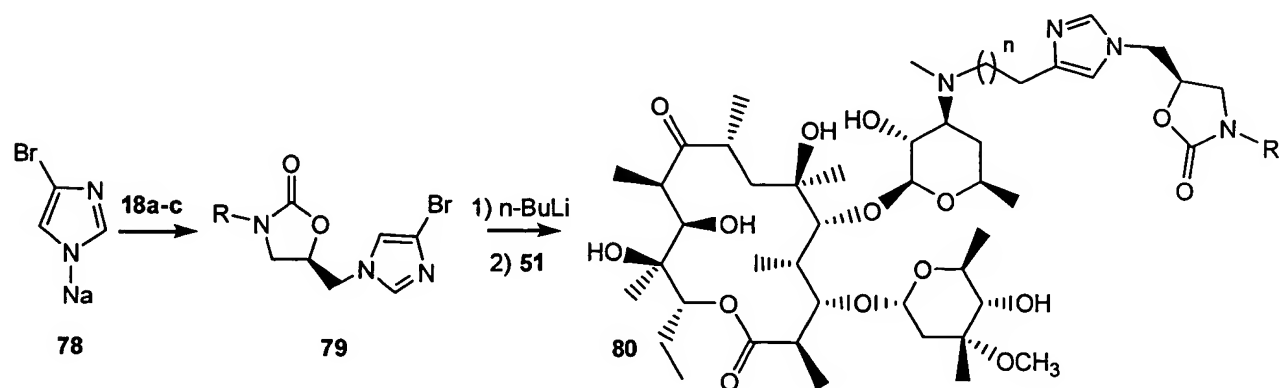
Scheme 12

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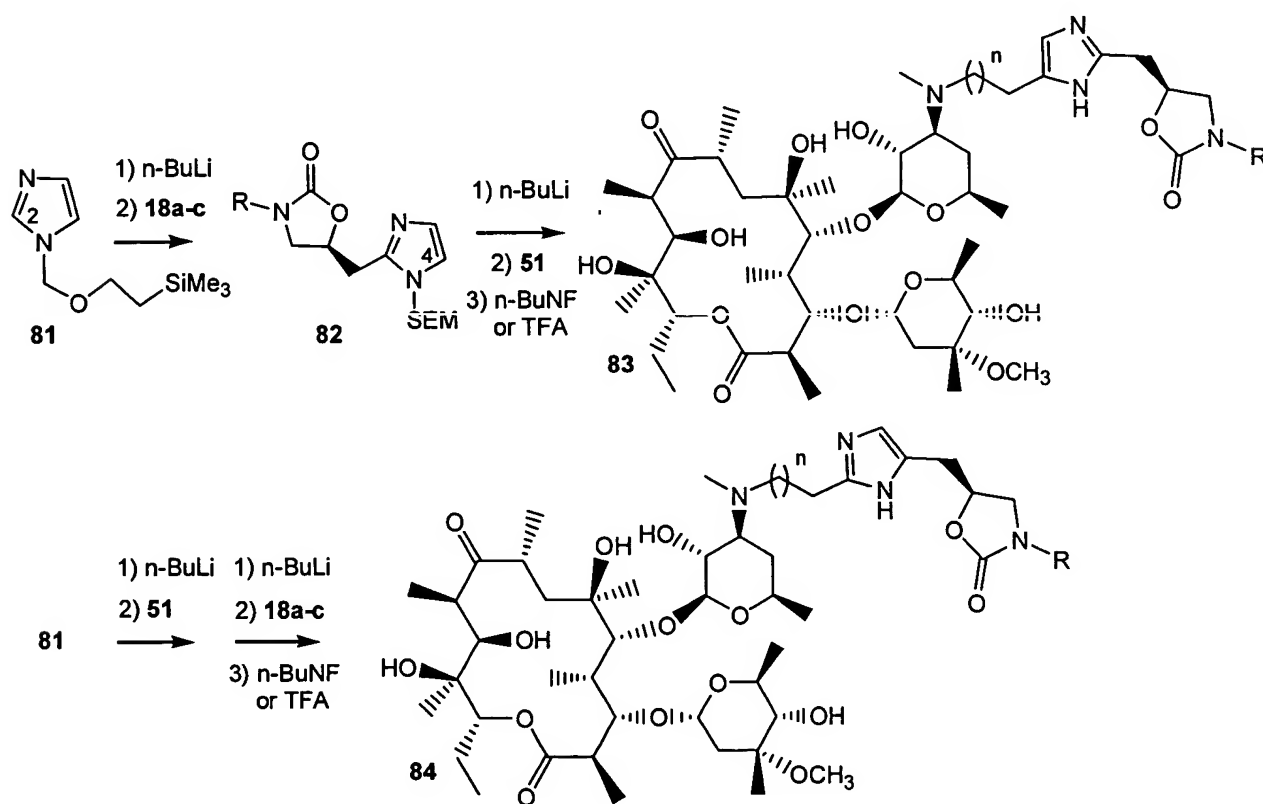
Scheme 13 illustrates another synthesis of imidazoles of the present invention. 4-Bromoimidazole can be deprotonated using, for example, sodium hydride or lithium diisopropylamide, or another suitable organic base, to give anion **78** (or the corresponding lithio derivative). Alkylation of **78** with **18a-c** can yield bromoimidazole **79** which can then be subjected to metal-halogen exchange and alkylated with **51** (or a suitably protected derivative of **51**) to produce isomeric 1,4-disubstituted imidazoles **80**.

15 Scheme 13



Scheme 14 depicts chemistry suitable for the synthesis of other target imidazole derivatives. The silylethoxymethyl (SEM) protected imidazole can be lithiated at C-2 (Shapiro *et al.* (1995) HETEROCYCLES 41: 215) and can react with electrophiles **18a-c** to produce imidazole intermediates **82**. Lithiation of imidazole intermediates **82** at C-4 of the imidazole, followed by alkylation with electrophiles of type **51** (or a suitably protected version such as the per-silylated derivative), and then deprotection of the SEM can produce imidazoles **83**.

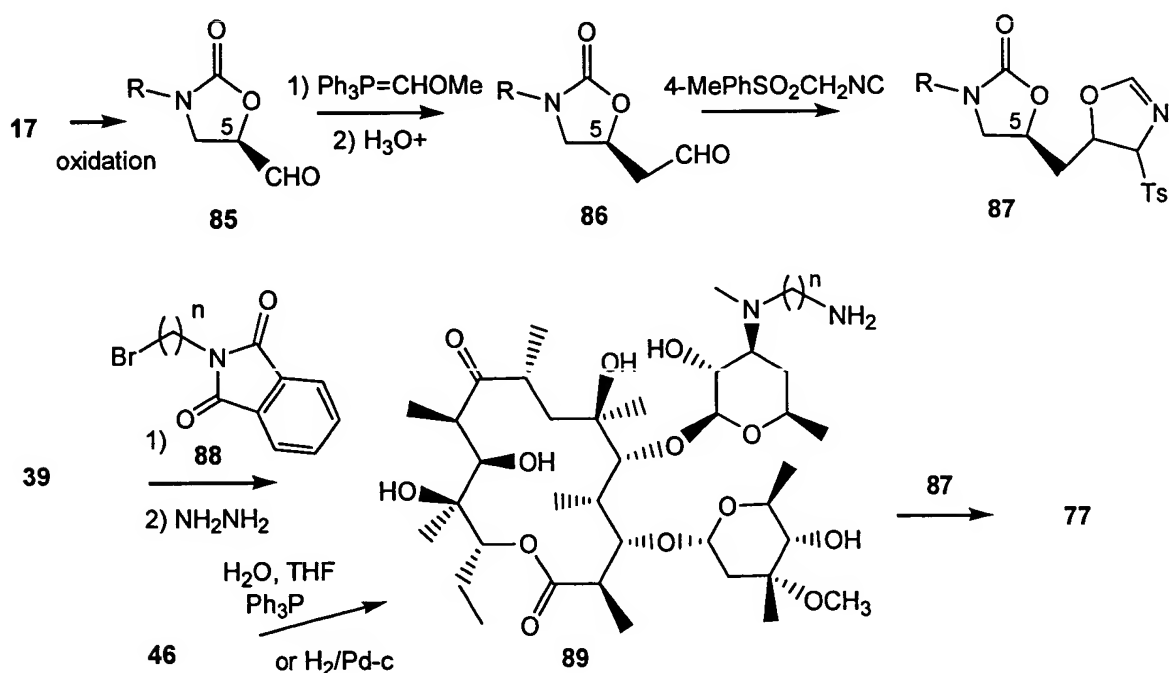
Scheme 14



Scheme 15 shows how tosylmethyl isocyanide can be used to make imidazoles of the present invention (Vanelle *et al.* (2000) EUR. J. MED. CHEM. 35: 157; Horne *et al.* (1994) HETEROCYCLES 39: 139). Alcohols **17** can be oxidized to produce aldehydes **85** using an appropriate agent such as the Dess-Martin periodinane, or oxalyl chloride/dimethylsulfoxide/triethylamine (Swern oxidation). A variety of chromium complexes can also be used for this oxidation, including, for example, pyridinium dichromate (PDC), pyridinium chlorochromate

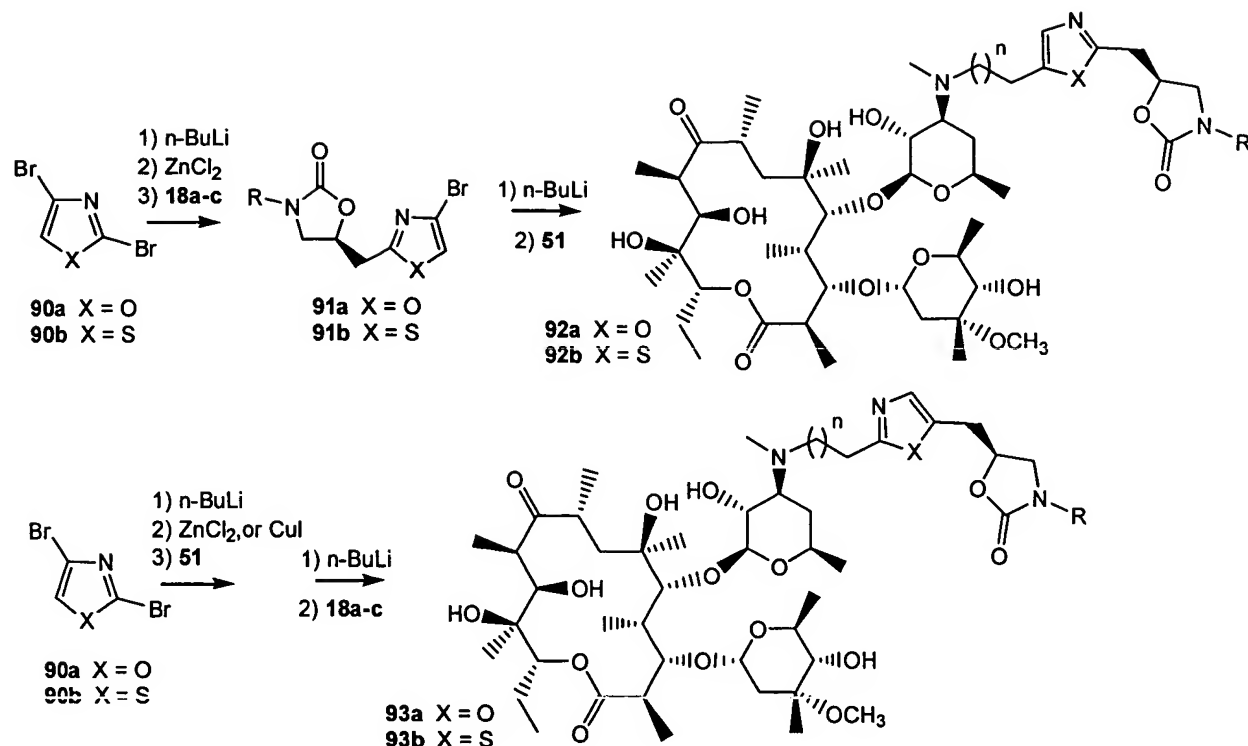
(PCC), chromium trioxide, and tetrapropylammonium perruthenate. Wittig homologation of **85** can provide aldehyde **86**, which can then be converted by tosylmethyl isocyanide to produce intermediate **87**. The reaction of **87** with amines **89** (formed via alkylation of amines **39** with bromoalkyl phthalimides **88** followed by hydrazine cleavage, or reduction of azides **46**) can produce imidazoles **77**.

Scheme 15



Scheme 16 delineates how 1,3 thiazole and 1,3 oxazole derivatives of the present invention can be synthesized. Known dibromo thiazoles and oxazoles **90a** and **90b** can be selectively metallated at C-2 and alkylated with electrophiles **18a-c** to produce intermediates **91a** and **91b** (Pinkerton *et al.* (1972) J. HETEROCYCLIC CHEMISTRY 9: 67). Transmetallation with zinc chloride can be employed in the case of the oxazole anion if the anion displays any tendency to ring open prior to its reaction with certain electrophiles. The bromo azoles **91** can be metallated to form the corresponding anion which can undergo alkylation with sulfonates **51** (or the related halides) to produce the final targets **92**. Reordering of the sequence of electrophiles in this process permits access to the isomeric thiazoles and oxazoles **93**.

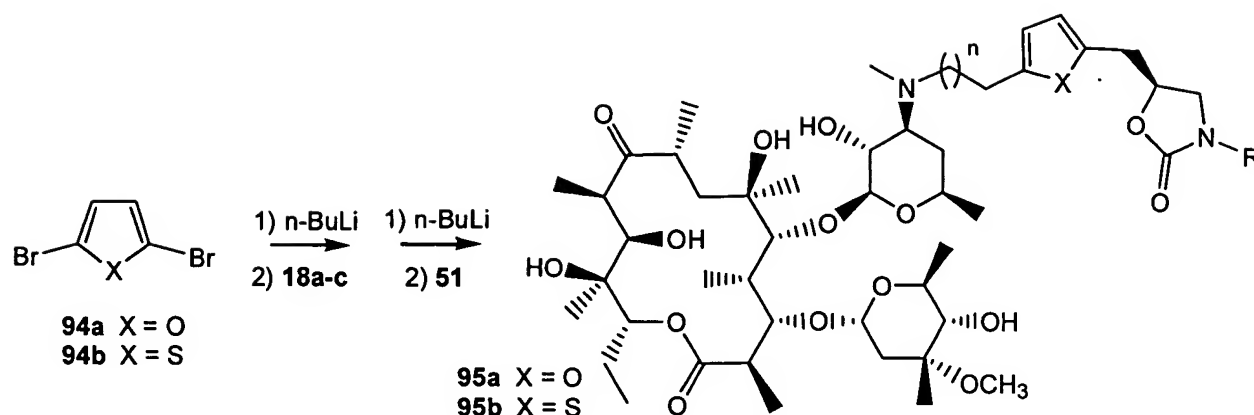
Scheme 16



5 Scheme 17 shows the synthesis of 2,5 disubstituted furan and thiophene derivatives of the invention. Commercially available dibromofuran **94a** and dibromothiophene **94b** can be monolithiated (Cherieux *et al.* (2001) ADVANCED FUNCTIONAL MATERIALS 11: 305) and alkylated with electrophiles **18a-c**. The monobromo intermediates obtained from this reaction can be lithiated again and then alkylated with electrophiles of type **51** (or a protected version of

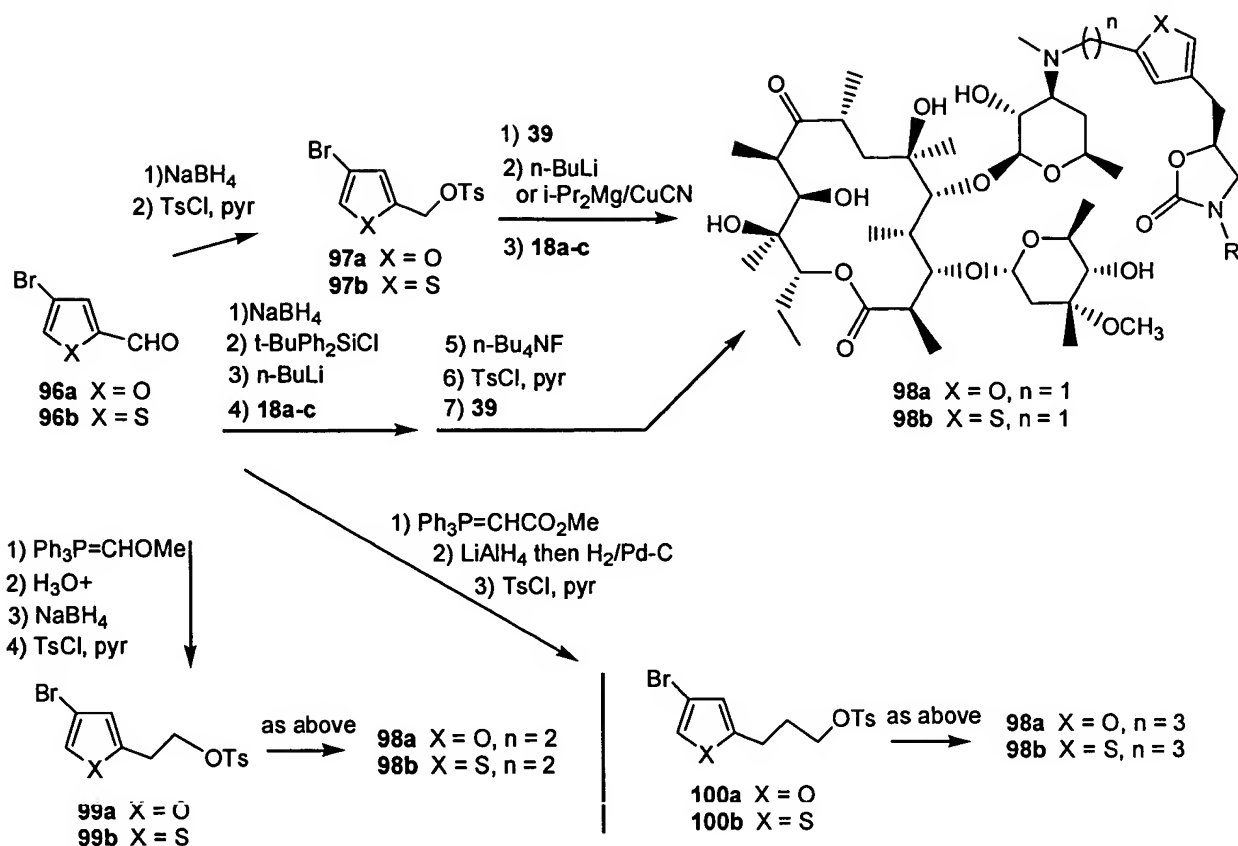
10 **51**) to produce the final targets **95**.

Scheme 17



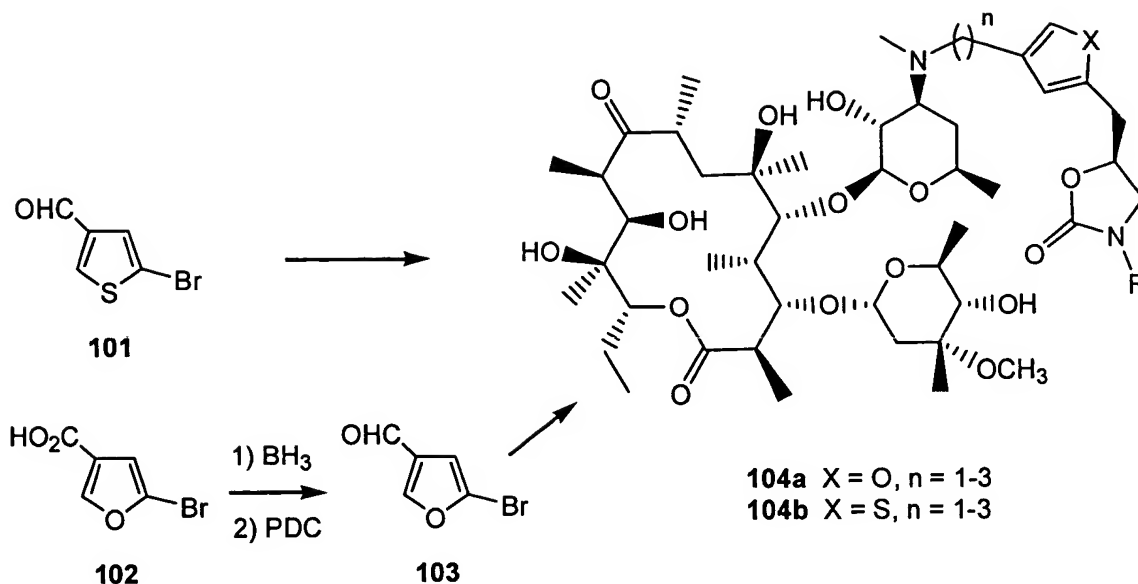
Scheme 18 depicts the synthesis of 2,4 disubstituted furan and thiophene derivatives of the invention. Commercially available furan aldehyde **96a**, and the known thiophene aldehyde **96b**, can be reduced to the corresponding alcohols and the resulting alcohols converted to a leaving group such as tosylates **97**. Alternate sulfonates and halides can be synthesized and used in this fashion. The tosylates **97** can alkylate amine **39** (or a protected version thereof), and the heteroaryl bromide can be converted to a suitable organometallic agent (by reagents such as n-BuLi, or i-Pr₂Mg/CuCN). This intermediate organometallic agent can be alkylated with electrophiles **18a-c** to produce targets of type **98** where n = 1. As the scheme shows, a reordering of steps can be employed involving reduction, silylation, lithiation and then initial alkylation with **18a-c**. Desilylation of the alkylation product, followed by tosylation of the alcohol, provides an intermediate that can then be alkylated with amine **39** to produce targets **98**. Simple homologation protocols, using the reagents depicted in Scheme 18 or others known to those skilled in the art, can convert the aldehydes **96** to longer chain tosylates such as **99** and **100**. The use of these tosylates in the alkylation with **39**, and subsequent metal-halogen exchange and alkylation with **18a-c**, can yield compounds of type **98** where n = 2 and 3. It will be appreciated that longer chain tosylates can be produced using chemistries similar to that depicted in Scheme 18, and that other bifunctional linkers can be used to produce compounds of type **98**.

Scheme 18



Chemistries similar to that employed above in Scheme 18 can convert known thiophene aldehyde **101** (Eras *et al.* (1984) J. HETEROCYCLIC CHEMISTRY 21: 215) to produce products of type **104** (Scheme 19). The known acid **102** (Wang *et al.* (1996) TETRAHEDRON 52: 12137) can be converted to aldehyde **103** by reduction with, for example, borane or lithium aluminum hydride, followed by oxidation of the resultant hydroxymethyl intermediate with, for example, PDC, PCC, or another suitable reagent. Aldehyde **103** can then be converted to produce compounds of type **104**.

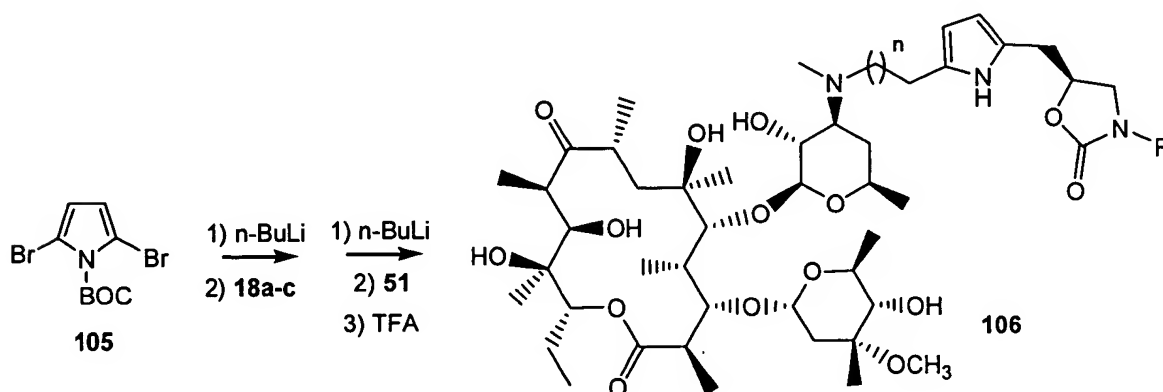
Scheme 19



5 Scheme 20 illustrates the synthesis of 2,5 disubstituted pyrroles of the invention. The BOC-protected dibromopyrrole **105** can be lithiated and alkylated sequentially (Chen *et al.* (1987) TETRAHEDRON LETT. 28: 6025; Chen *et al.* (1992) ORG. SYNTH. 70: 151; and Martina *et al.* (1991) SYNTHESIS 613), and allowed to react with electrophiles **18a-c** and **51** (or a suitably protected analogue of **51**) to produce, after final BOC deprotection with TFA,

10 disubstituted pyrroles of type **106**.

Scheme 20

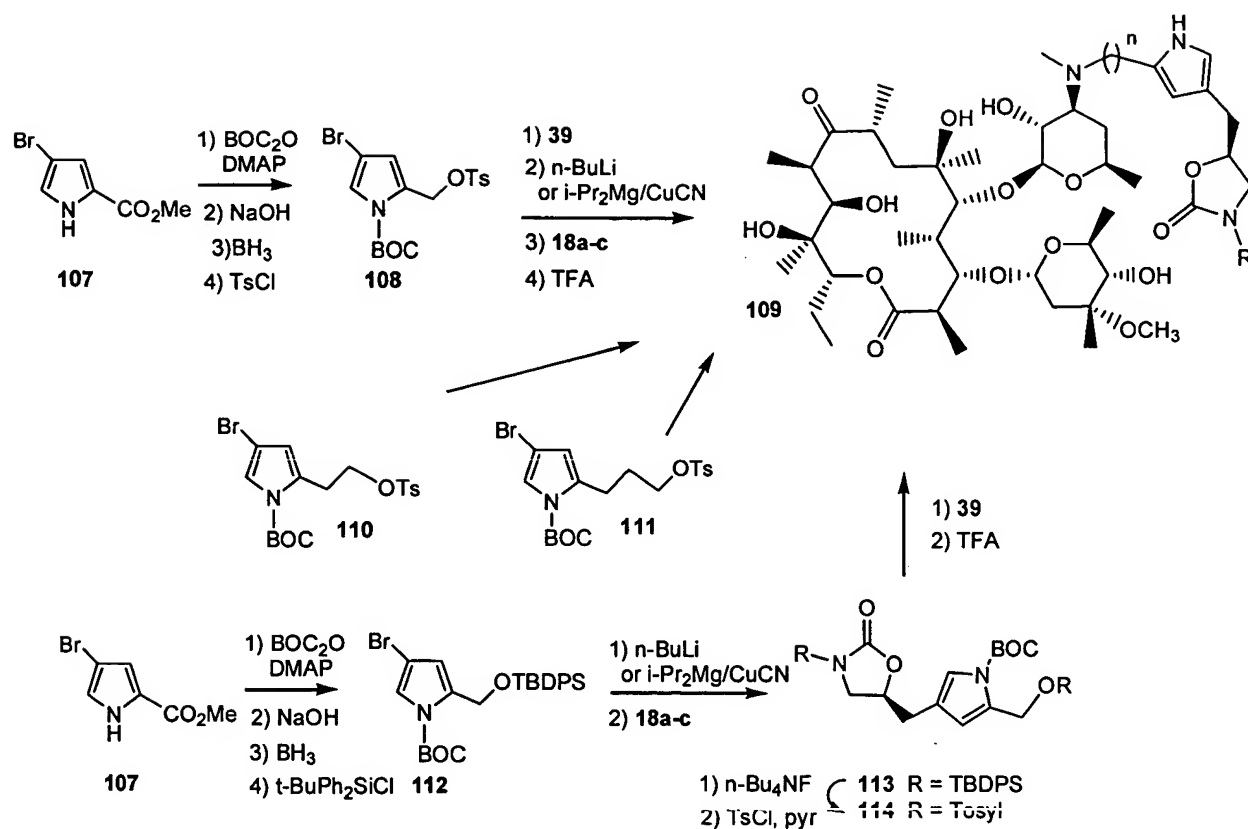


Scheme 21 shows the synthesis of 2,4 disubstituted pyrroles of the invention.

Commercially available pyrrole ester **107** can be protected with a suitable protecting group, for example, the BOC group, and the ester function hydrolyzed to the corresponding acid. The resulting acid can then be reduced to the alcohol using, for example, borane to yield an alcohol that can be converted to tosylate **108**. Amine **39** (or a suitably protected version of **39**, formed for example by silylation of the hydroxyl groups with bis-trimethylsilylacetamide or another silylating reagent) can be alkylated with tosylate **108** to produce an intermediate bromopyrrole. The bromopyrrole can then be converted to an organometallic reagent that can then react with electrophiles **18a-c**. The resulting product can then be deprotected with TFA to produce pyrroles **109**. The alcohol formed after borane reduction of the acid derived from **107** can then be homologated to tosylates **110** and **111** by chemistries similar to that shown below in Scheme 23. The use of these tosylates in the alkylation strategy can produce target pyrroles of type **109** where $n = 2$ and 3 .

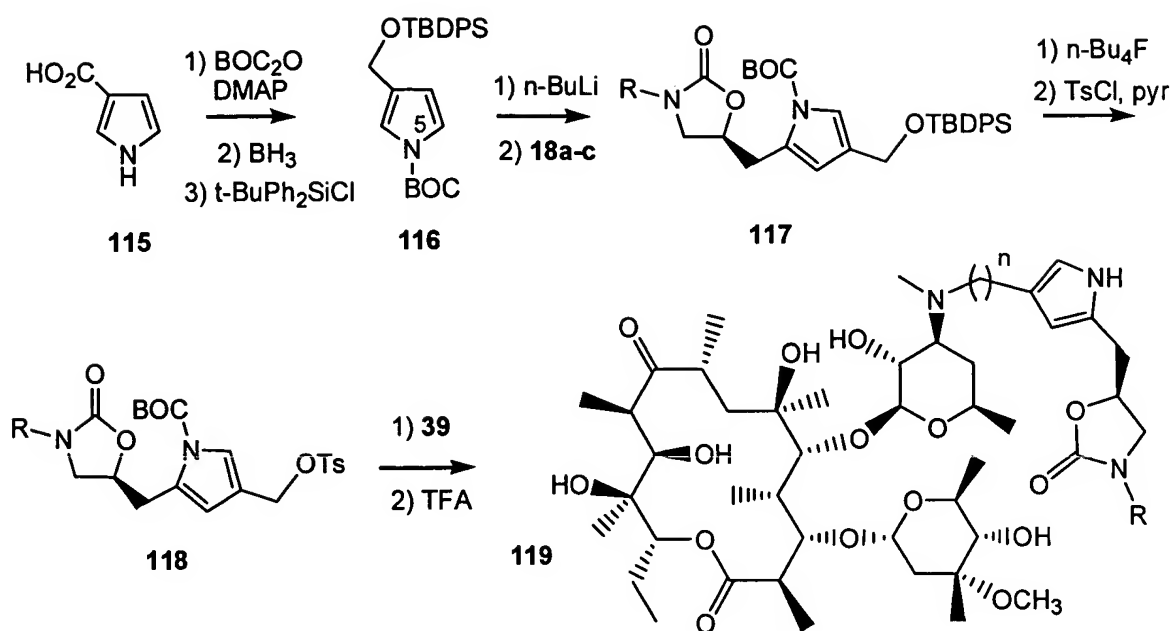
An alternative approach is to protect the alcohol functions prior to tosylation, and perform the alkylation of the organometallic derived from the halopyrrole with **18a-c** first. For example, silyloxy derivative **112** can be produced from **107**, and the organometallic derivative derived from it alkylated with **18a-c** to yield silyl ethers **113**. Subsequent desilylation and conversion to tosylates **114** provides an electrophile that can be used in the alkylation reaction with **39**. A final BOC cleavage can then give pyrroles **109**. It is understood that the alcohol precursor of **112** can be homologated, using chemistries similar to that shown below in Scheme 23 and other schemes) to other alkanols that can be tosylated for further reactions with amine **39** (or related macrolide derived amines). Furthermore, the alcohol derived from silyl cleavage of **113** can serve as the starting material for this type of homologation efforts to produce the alkyl tosylates (or halides) required for making targets **109** where n is variable.

Scheme 21



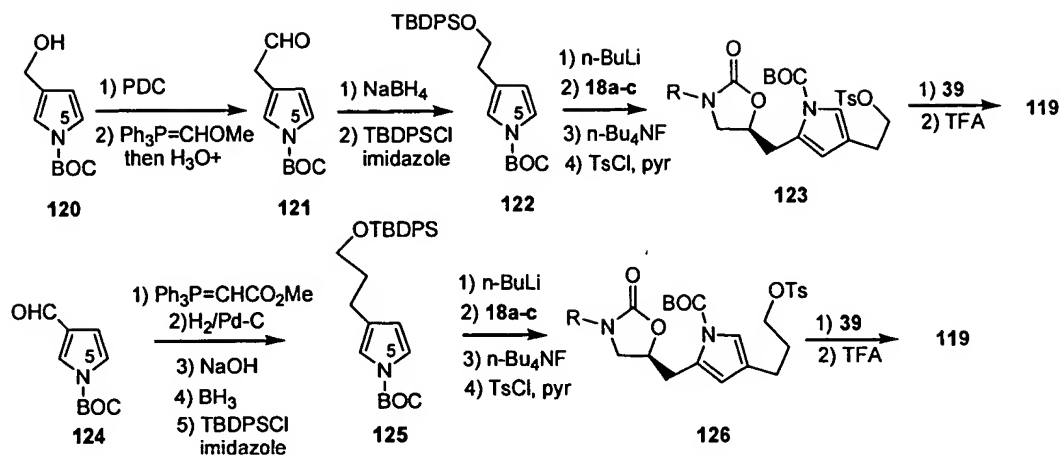
Scheme 22 shows the synthesis of isomeric 2,4-disubstituted pyrroles of the invention. Commercially available pyrrole acid **115** can be protected as the BOC derivative, and the acid function reduced to an alcohol, which can then be protected to produce the silyl ether **116**. Deprotonation of **116** with *n*-butyllithium can occur at the 5 position of the pyrrole ring, and this anion (or that derived from transmetallation with an appropriate metal) can be alkylated with electrophiles **18a-c** to produce pyrrole **117**. Desilylation of **117**, followed by tosylation, alkylation with amine **39**, and TFA deprotection of the BOC group can yield pyrroles **119**.

Scheme 22



Scheme 23 illustrates the synthesis of longer chain tosylates of type **123** and **126** used to alkylate amines of type **39** to produce pyrroles **119**. The alcohol **120** derived from protection of **115** followed by borane reduction can be oxidized to aldehyde **124**. The Wittig reaction of aldehyde **124** with methoxymethyl triphenylphosphorane is followed by an acid hydrolysis step to produce the homologated aldehyde **121**. Reduction and silyl protection can yield **122**, which can then be deprotonated, alkylated and then converted to tosylate **123**. Aldehyde **124** can undergo a Wittig reaction with carbomethoxymethyl triphenylphosphorane. The Wittig product then is reduced to an alkanol that can then be silylated to produce **125**. Conversion of **125** to pyrroles **119** can then occur using the same chemistry employed to provide **119** from **122**.

Scheme 23



Scheme 24 shows the synthesis of 1,3 disubstituted pyrroles of the present invention.

The BOC group of **116** can be cleaved to produce free pyrrole **127**. Alkylation of **127** (in a

5 suitable organic solvent such as DMF) with **18a-c** can produce intermediate **128**. The dianion of

3-hydroxymethylpyrrole can also be suitable for alkylation with **18a-c** to produce the free

hydroxy derivative of silyl ether **128**. Conversion of the siloxy group to the corresponding

tosylate, followed by alkylation with amines of type **39** can generate the target N-substituted

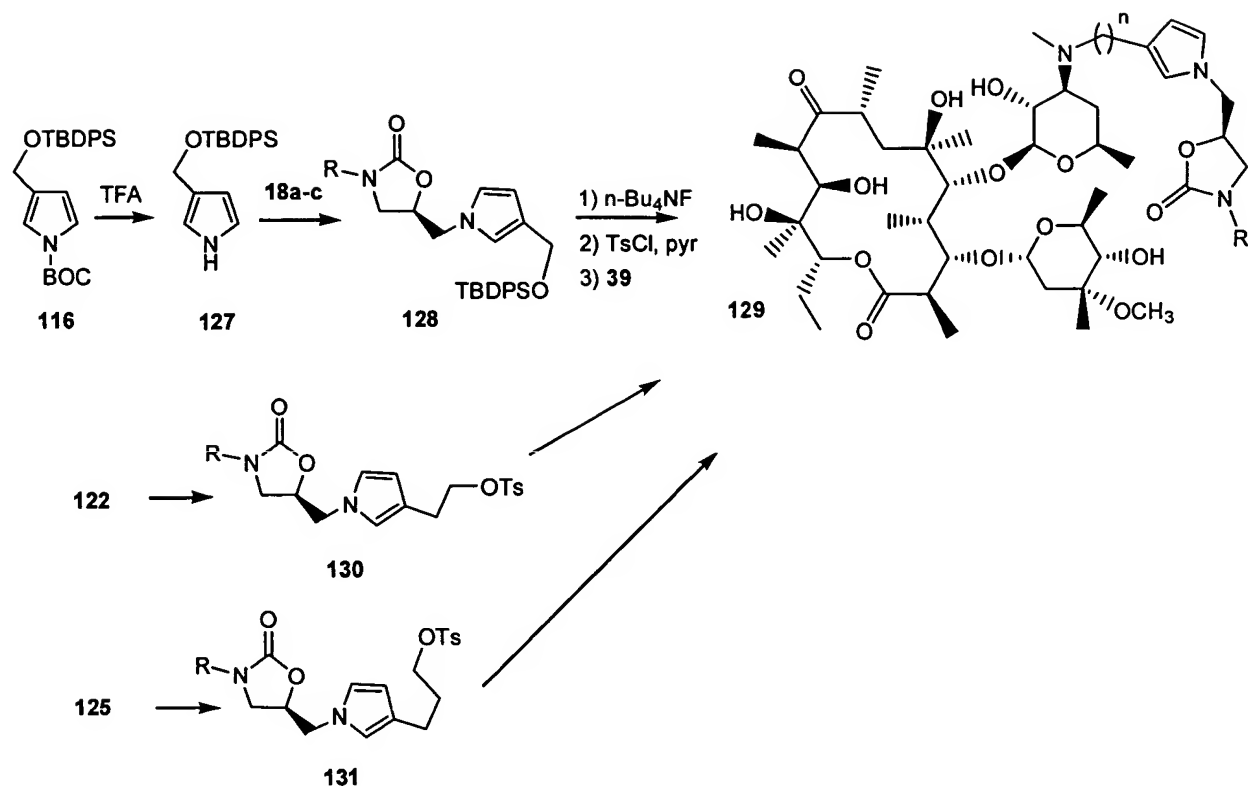
pyrroles **129** (where $n = 1$). In a similar fashion, the BOC pyrroles **122** and **125** can be converted

10 to the tosylates **130** and **131**. These tosylates can be used to produce pyrroles of type **129** (where

$n = 2$ and 3). It is understood that longer chain alkyl tosylates (and halides) can be produced that

can undergo this chemistry to produce pyrroles **129** where n is > 3 .

Scheme 24

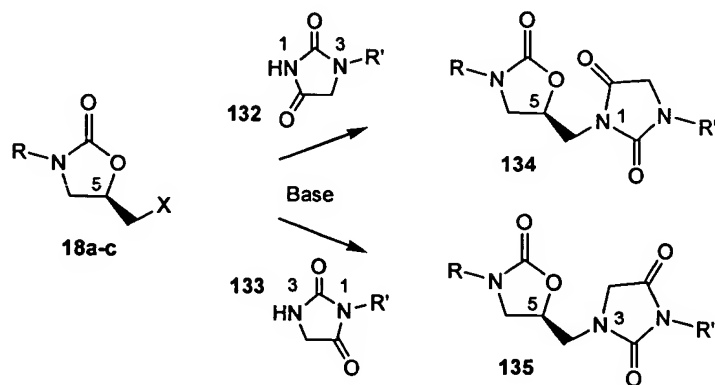


Scheme 25 illustrates the use of hydantoin-like groups as the 5-membered heterocyclic linker between the G groups and the R₁ moieties of the present invention. Electrophiles of type 18a-c can alkylate anions derived from hydantoins to produce compounds of the present invention. For example, 3-substituted hydantoins of type 132 can be purchased and treated with an appropriate base to generate the corresponding imide anion. The resulting anions can be alkylated with electrophiles similar (but not limited) to intermediates 18a-c to produce hydantoin derivatives 134. Alternatively, 1-substituted hydantoins of type 133 can be purchased or prepared, and treated with base and electrophile to yield isomeric hydantoin derivatives 135. It is understood that such hydantoins can have, for example, at optional locations, thiocarbonyl functionalities in place of the illustrated carbonyl groups. Such compounds can be prepared by treatment of the oxy-hydantoins with Lawesson's reagent, elemental sulfur, phosphorus pentasulfide, and other reagents commonly used in the art to perform this transformation.

Alternatively, such thiohydantoins can be synthesized selectively by sequential synthetic steps known in the art. The R' group of 132 and 133 may represent a protecting group function, for example, benzyl, alkoxybenzyl, benzyloxycarbonyl, t-butoxycarbonyl, that is compatible with the alkylation step. Such a protecting group can subsequently be removed from products

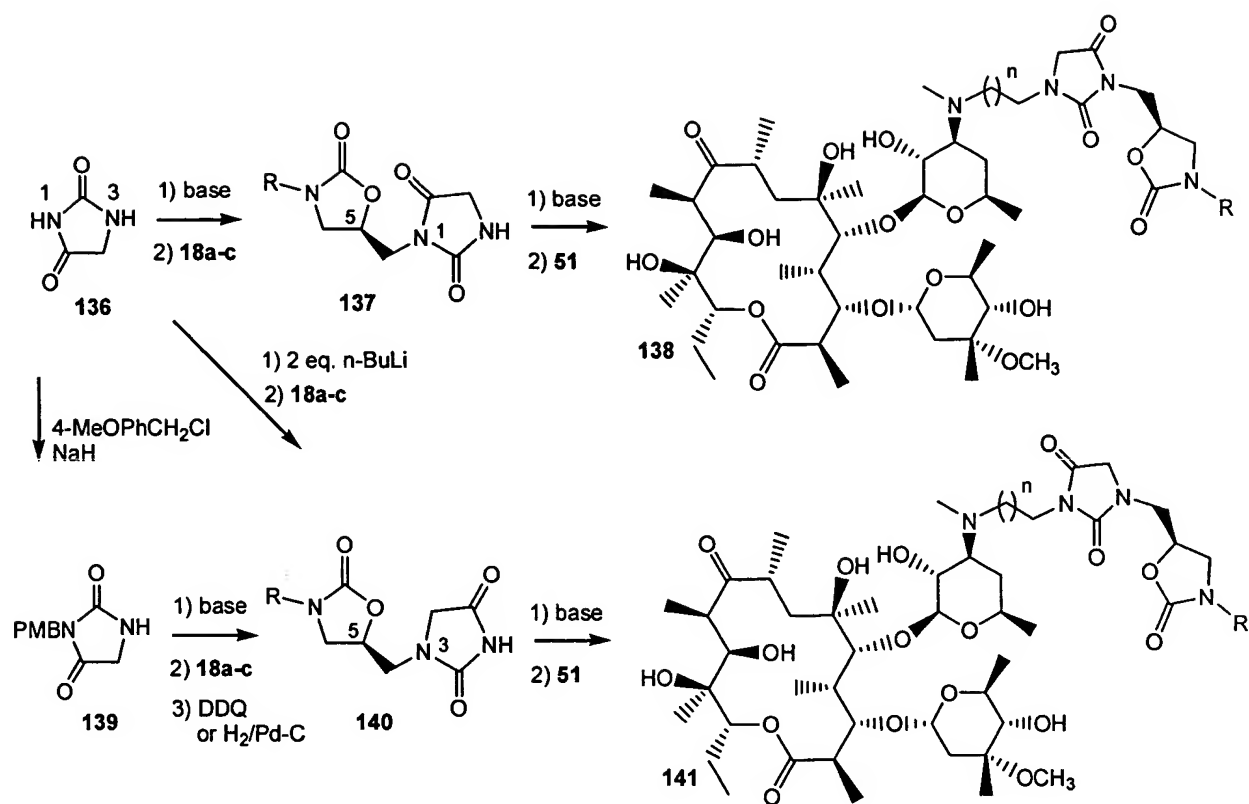
134 and **135**, yielding products where the R' group is a hydrogen atom. These intermediates can be used to produce various target molecules by their treatment with base and then subsequent exposure to appropriate electrophiles.

5 Scheme 25



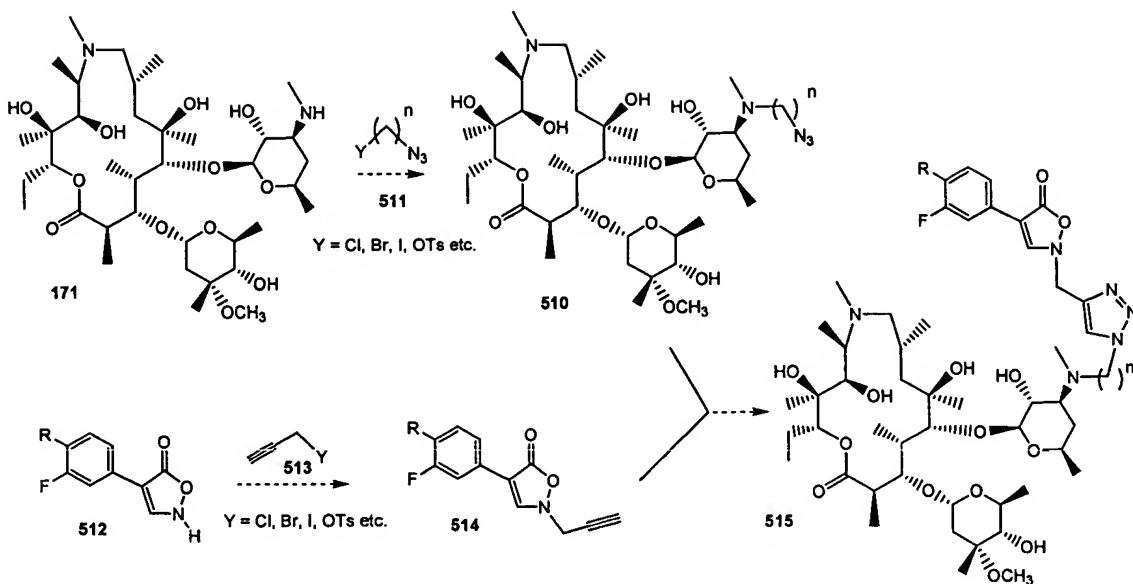
A more specific example of the synthesis of hydantoin derivatives of the present invention is depicted in Scheme 26. Hydantoin **136** can be treated with a mild organic base, for example, sodium hydride, potassium tertiary-butoxide, cesium, sodium, or potassium carbonate, to produce the N-1 substituted intermediate **137**. Deprotonation of **137** with a base, for example, sodium hydride, n-butyllithium, lithium bis-trimethylsilylamide or lithium diisopropylamide, followed by alkylation with **51** (or a suitably protected derivative of **51**) can yield hydantoin targets of type **138**. The isomeric hydantoin derivatives of type **141** can be synthesized from **136** by initial p-methoxybenzyl (PMB) protection of the N-1 position, followed by alkylation at N-3 with **18a-c** and subsequent deprotection of the PMB group with either 2,3-dichloro-3,4-dicyano-benzoquinone (DDQ) or hydrogenation will yield hydantoin intermediates **140**. Subsequent alkylation of **140** with **51** can give compounds **141**. Another route to produce intermediates **140** is by formation of the dianion of hydantoin **136**. One equivalent of a weak base can deprotonate the N-1 position of **136**. The addition of another equivalent of a strong base, for example, n-butyllithium, to the initial anion can deprotonate it again, this time at N-3. Alkylation can occur at the more reactive position (N-3) to again produce hydantoins **140**.

Scheme 26



Scheme 27 illustrates how isoxazolidinone derivatives of type **515** of the present invention can be synthesized. Macrolide **171** (or any other macrolide amine) can be converted to alkyl azide **510** (where $n \geq 2$) via use of an appropriate alkyl halide or sulfonate electrophile of type **511**. A variety of isoxazolidinone derivatives of type **512** (for syntheses of these types of derivatives see US Patent Application 20020094984) can be alkylated with propargyl electrophiles of type **513** to yield alkynes of type **514**. The cycloaddition of azides **510** and alkynes **514** yields target isoxazolidinone derivatives **515**. It is to be understood that alternative macrolides and isoxazolidinone derivatives can be used in this chemistry, and alternate chain lengths of the various electrophiles can be utilized to produce other compounds of the present invention. It is intended that such alternate targets are within the scope of the present invention.

Scheme 27



In addition to the foregoing, compounds disclosed in the following publications, patents and patent applications are suitable intermediates for preparation of the compounds of this

5 invention:

Tucker, J.A. *et al.*, *J. Med. Chem.*, **1998**, *41*, 3727; Gregory, W.A. *et al.*, *J. Med. Chem.*, **1990**, *33*, 2569; Genin, M.J. *et al.*, *J. Med. Chem.*, **1998**, *41*, 5144; Brickner, S.J. *et al.*, *J. Med. Chem.*, **1996**, *39*, 673. Barbachyn, M.R. *et al.*, *J. Med. Chem.*, **1996**, *39*, 680; Barbachyn, M.R. *et al.*, *Bioorg. Med. Chem. Lett.*, **1996**, *6*, 1003; Barbachyn, M.R. *et al.*, *Bioorg. Med. Chem. Lett.*, **1996**, *6*, 1009; Grega, K.C. *et al.*, *J. Org. Chem.*, **1995**, *60*, 5255; Park, C.-H. *et al.*, *J. Med. Chem.*, **1992**, *35*, 1156; Yu, D. *et al.*, *Bioorg. Med. Chem. Lett.*, **2002**, *12*, 857; Weidner-Wells, M.A. *et al.*, *Bioorg. Med. Chem.*, **2002**, *10*, 2345; and Cacchi, S. *et al.*, *Org. Lett.*, **2001**, *3*, 2539.

U.S. Pat. Nos. 4,801,600; 4,948, 801; 5,736,545; 6,362,189; 5,523,403; 4,461,773; 6,365,751; 6,124,334; 6,239,152; 5,981,528; 6,194,441; 6,147,197; 6,034,069; 4,990,602; 6,124,269; and 6,271,383. U.S. Pat. Application 2001/0046992, PCT Application and publications

WO96/15130; WO95/14684; WO 99/28317; WO 98/01447; WO 98/01446; WO 97/31917; WO 97/27188; WO 97/10223; WO 97/09328; WO 01/46164; WO 01/09107; WO 00/73301; WO 00/21960; WO 01/81350; WO 97/30995; WO 99/10342; WO 99/10343; WO 99/64416; WO 00/232917; and WO 99/64417, European Patents EP 0312000 B1; EP 0359418 A1; EP

00345627; EP 1132392; and EP 0738726 A1.

4. Characterization of Compounds of the Invention

Compounds designed, selected and/or optimized by methods described above, once produced, may be characterized using a variety of assays known to those skilled in the art to determine whether the compounds have biological activity. For example, the molecules may be characterized by conventional assays, including but not limited to those assays described below, to determine whether they have a predicted activity, binding activity and/or binding specificity.

Furthermore, high-throughput screening may be used to speed up analysis using such assays. As a result, it may be possible to rapidly screen the molecules described herein for activity, for example, as anti-cancer, anti-bacterial, anti-fungal, anti-parasitic or anti-viral agents.

Also, it may be possible to assay how the compounds interact with a ribosome or ribosomal subunit and/or are effective as modulators (for example, inhibitors) of protein synthesis using techniques known in the art. General methodologies for performing high-throughput screening are described, for example, in Devlin (1998) High Throughput Screening, Marcel Dekker; and U.S. Patent No. 5,763,263. High-throughput assays can use one or more different assay techniques including, but not limited to, those described below.

(1) *Surface Binding Studies*. A variety of binding assays may be useful in screening new molecules for their binding activity. One approach includes surface plasmon resonance (SPR) which can be used to evaluate the binding properties molecules of interest with respect to a ribosome, ribosomal subunit or a fragment thereof.

SPR methodologies measure the interaction between two or more macromolecules in real-time through the generation of a quantum-mechanical surface plasmon. One device, (BIAcore Biosensor RTM from Pharmacia Biosensor, Piscataway, N.J.) provides a focused beam of polychromatic light to the interface between a gold film (provided as a disposable biosensor "chip") and a buffer compartment that can be regulated by the user. A 100 nm thick "hydrogel" composed of carboxylated dextran which provides a matrix for the covalent immobilization of analytes of interest is attached to the gold film. When the focused light interacts with the free electron cloud of the gold film, plasmon resonance is enhanced. The resulting reflected light is spectrally depleted in wavelengths that optimally evolved the resonance. By separating the reflected polychromatic light into its component wavelengths (by means of a prism), and determining the frequencies which are depleted, the BIAcore establishes an optical interface which accurately reports the behavior of the generated surface plasmon resonance. When

designed as above, the plasmon resonance (and thus the depletion spectrum) is sensitive to mass in the evanescent field (which corresponds roughly to the thickness of the hydrogel). If one component of an interacting pair is immobilized to the hydrogel, and the interacting partner is provided through the buffer compartment, the interaction between the two components can be measured in real time based on the accumulation of mass in the evanescent field and its corresponding effects of the plasmon resonance as measured by the depletion spectrum. This system permits rapid and sensitive real-time measurement of the molecular interactions without the need to label either component.

(2) *Fluorescence Polarization*. Fluorescence polarization (FP) is a measurement technique that can readily be applied to protein-protein, protein-ligand, or RNA-ligand interactions in order to derive IC_{50} s and K_d s of the association reaction between two molecules. In this technique one of the molecules of interest is conjugated with a fluorophore. This is generally the smaller molecule in the system (in this case, the compound of interest). The sample mixture, containing both the ligand-probe conjugate and the ribosome, ribosomal subunit or fragment thereof, is excited with vertically polarized light. Light is absorbed by the probe fluorophores, and re-emitted a short time later. The degree of polarization of the emitted light is measured. Polarization of the emitted light is dependent on several factors, but most importantly on viscosity of the solution and on the apparent molecular weight of the fluorophore. With proper controls, changes in the degree of polarization of the emitted light depends only on changes in the apparent molecular weight of the fluorophore, which in-turn depends on whether the probe-ligand conjugate is free in solution, or is bound to a receptor. Binding assays based on FP have a number of important advantages, including the measurement of IC_{50} s and K_d s under true homogenous equilibrium conditions, speed of analysis and amenity to automation, and ability to screen in cloudy suspensions and colored solutions.

(3) *Protein Synthesis*. It is contemplated that, in addition to characterization by the foregoing biochemical assays, the compound of interest may also be characterized as a modulator (for example, an inhibitor of protein synthesis) of the functional activity of the ribosome or ribosomal subunit.

Furthermore, more specific protein synthesis inhibition assays may be performed by administering the compound to a whole organism, tissue, organ, organelle, cell, a cellular or subcellular extract, or a purified ribosome preparation and observing its pharmacological and

inhibitory properties by determining, for example, its inhibition constant (IC_{50}) for inhibiting protein synthesis. Incorporation of 3H leucine or ^{35}S methionine, or similar experiments can be performed to investigate protein synthesis activity. A change in the amount or the rate of protein synthesis in the cell in the presence of a molecule of interest indicates that the molecule is a modulator of protein synthesis. A decrease in the rate or the amount of protein synthesis indicates that the molecule is a inhibitor of protein synthesis.

Furthermore, the compounds may be assayed for anti-proliferative or anti-infective properties on a cellular level. For example, where the target organism is a micro-organism, the activity of compounds of interest may be assayed by growing the micro-organisms of interest in media either containing or lacking the compound. Growth inhibition may be indicative that the molecule may be acting as a protein synthesis inhibitor. More specifically, the activity of the compounds of interest against bacterial pathogens may be demonstrated by the ability of the compound to inhibit growth of defined strains of human pathogens. For this purpose, a panel of bacterial strains can be assembled to include a variety of target pathogenic species, some containing resistance mechanisms that have been characterized. Use of such a panel of organisms permits the determination of structure-activity relationships not only in regards to potency and spectrum, but also with a view to obviating resistance mechanisms. The assays may be performed in microtiter trays according to conventional methodologies as published by The National Committee for Clinical Laboratory Standards (NCCLS) guidelines (NCCLS. M7-A5- Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically; Approved Standard-Fifth Edition. NCCLS Document M100-S12/M7 (ISBN 1-56238-394-9).

The compounds may be assayed for anti-inflammatory properties on a cellular level, for example, to determine the inhibition of cytokine production. Further, the compounds may be assessed for calcium flux in CHO cells expressing the human motilin receptor or in animal models for prokinetic behavior such as the rabbit duodenum strip model known to display contractility when a motilin agonist is applied.

5. Formulation and Administration

The compounds of the invention may be useful in the prevention or treatment of a variety of human or other animal disorders, including for example, bacterial infection, fungal infections, viral infections, parasitic diseases, and cancer. It is contemplated that, once identified, the active

molecules of the invention may be incorporated into any suitable carrier prior to use. The dose of active molecule, mode of administration and use of suitable carrier will depend upon the intended recipient and target organism. The formulations, both for veterinary and for human medical use, of compounds according to the present invention typically include such compounds in association with a pharmaceutically acceptable carrier.

The carrier(s) should be "acceptable" in the sense of being compatible with the other ingredients of the formulations and not deleterious to the recipient. Pharmaceutically acceptable carriers, in this regard, are intended to include any and all solvents, dispersion media, coatings, anti-bacterial and anti-fungal agents, isotonic and absorption delaying agents, and the like, compatible with pharmaceutical administration. The use of such media and agents for pharmaceutically active substances is known in the art. Except insofar as any conventional media or agent is incompatible with the active compound, use thereof in the compositions is contemplated. Supplementary active compounds (identified or designed according to the invention and/or known in the art) also can be incorporated into the compositions. The formulations may conveniently be presented in dosage unit form and may be prepared by any of the methods well known in the art of pharmacy/microbiology. In general, some formulations are prepared by bringing the compound into association with a liquid carrier or a finely divided solid carrier or both, and then, if necessary, shaping the product into the desired formulation.

A pharmaceutical composition of the invention should be formulated to be compatible with its intended route of administration. Examples of routes of administration include oral or parenteral, for example, intravenous, intradermal, inhalation, transdermal (topical), transmucosal, and rectal administration. Solutions or suspensions used for parenteral, intradermal, or subcutaneous application can include the following components: a sterile diluent such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylenediaminetetraacetic acid; buffers such as acetates, citrates or phosphates and agents for the adjustment of tonicity such as sodium chloride or dextrose. pH can be adjusted with acids or bases, such as hydrochloric acid or sodium hydroxide.

Useful solutions for oral or parenteral administration can be prepared by any of the methods well known in the pharmaceutical art, described, for example, in Remington's

Pharmaceutical Sciences, (Gennaro, A., ed.), Mack Pub., (1990). Formulations for parenteral administration can also include glycocholate for buccal administration, methoxysalicylate for rectal administration, or citric acid for vaginal administration. The parenteral preparation can be enclosed in ampoules, disposable syringes or multiple dose vials made of glass or plastic.

5 Suppositories for rectal administration also can be prepared by mixing the drug with a non-irritating excipient such as cocoa butter, other glycerides, or other compositions which are solid at room temperature and liquid at body temperatures. Formulations also can include, for example, polyalkylene glycols such as polyethylene glycol, oils of vegetable origin, hydrogenated naphthalenes, and the like. Formulations for direct administration can include
10 glycerol and other compositions of high viscosity. Other potentially useful parenteral carriers for these drugs include ethylene-vinyl acetate copolymer particles, osmotic pumps, implantable infusion systems, and liposomes. Formulations for inhalation administration can contain as excipients, for example, lactose, or can be aqueous solutions containing, for example, polyoxyethylene-9-lauryl ether, glycocholate and deoxycholate, or oily solutions for
15 administration in the form of nasal drops, or as a gel to be applied intranasally. Retention enemas also can be used for rectal delivery.

Formulations of the present invention suitable for oral administration may be in the form of: discrete units such as capsules, gelatin capsules, sachets, tablets, troches, or lozenges, each containing a predetermined amount of the drug; a powder or granular composition; a solution or
20 a suspension in an aqueous liquid or non-aqueous liquid; or an oil-in-water emulsion or a water-in-oil emulsion. The drug may also be administered in the form of a bolus, electuary or paste. A tablet may be made by compressing or moulding the drug optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing, in a suitable machine, the drug in a free-flowing form such as a powder or granules, optionally mixed by a binder,
25 lubricant, inert diluent, surface active or dispersing agent. Moulded tablets may be made by moulding, in a suitable machine, a mixture of the powdered drug and suitable carrier moistened with an inert liquid diluent.

Oral compositions generally include an inert diluent or an edible carrier. For the purpose of oral therapeutic administration, the active compound can be incorporated with excipients.
30 Oral compositions prepared using a fluid carrier for use as a mouthwash include the compound in the fluid carrier and are applied orally and swished and expectorated or swallowed.

Pharmaceutically compatible binding agents, and/or adjuvant materials can be included as part of the composition. The tablets, pills, capsules, troches and the like can contain any of the following ingredients, or compounds of a similar nature: a binder such as microcrystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose; a disintegrating agent
5 such as alginic acid, Primogel, or corn starch; a lubricant such as magnesium stearate or Sterotes; a glidant such as colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; or a flavoring agent such as peppermint, methyl salicylate, or orange flavoring.

Pharmaceutical compositions suitable for injectable use include sterile aqueous solutions (where water soluble) or dispersions and sterile powders for the extemporaneous preparation of
10 sterile injectable solutions or dispersion. For intravenous administration, suitable carriers include physiological saline, bacteriostatic water, Cremophor ELTM (BASF, Parsippany, NJ) or phosphate buffered saline (PBS). It should be stable under the conditions of manufacture and storage and should be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example,
15 water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. In many cases, it will be preferable to include isotonic agents, for example, sugars, polyalcohols such as manitol, sorbitol, sodium chloride in
20 the composition. Prolonged absorption of the injectable compositions can be brought about by including in the composition an agent which delays absorption, for example, aluminum monostearate and gelatin.

Sterile injectable solutions can be prepared by incorporating the active compound in the required amount in an appropriate solvent with one or a combination of ingredients enumerated
25 above, as required, followed by filter sterilization. Generally, dispersions are prepared by incorporating the active compound into a sterile vehicle which contains a basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, methods of preparation include vacuum drying and freeze-drying which yields a powder of the active ingredient plus any
30 additional desired ingredient from a previously sterile-filtered solution thereof.

Formulations suitable for intra-articular administration may be in the form of a sterile aqueous preparation of the drug which may be in microcrystalline form, for example, in the form of an aqueous microcrystalline suspension. Liposomal formulations or biodegradable polymer systems may also be used to present the drug for both intra-articular and ophthalmic administration.

Formulations suitable for topical administration, including eye treatment, include liquid or semi-liquid preparations such as liniments, lotions, gels, applicants, oil-in-water or water-in-oil emulsions such as creams, ointments or pastes; or solutions or suspensions such as drops. Formulations for topical administration to the skin surface can be prepared by dispersing the drug with a dermatologically acceptable carrier such as a lotion, cream, ointment or soap. Particularly useful are carriers capable of forming a film or layer over the skin to localize application and inhibit removal. For topical administration to internal tissue surfaces, the agent can be dispersed in a liquid tissue adhesive or other substance known to enhance adsorption to a tissue surface. For example, hydroxypropylcellulose or fibrinogen/thrombin solutions can be used to advantage. Alternatively, tissue-coating solutions, such as pectin-containing formulations can be used.

For inhalation treatments, inhalation of powder (self-propelling or spray formulations) dispensed with a spray can, a nebulizer, or an atomizer can be used. Such formulations can be in the form of a fine powder for pulmonary administration from a powder inhalation device or self-propelling powder-dispensing formulations. In the case of self-propelling solution and spray formulations, the effect may be achieved either by choice of a valve having the desired spray characteristics (*i.e.*, being capable of producing a spray having the desired particle size) or by incorporating the active ingredient as a suspended powder in controlled particle size. For administration by inhalation, the compounds also can be delivered in the form of an aerosol spray from pressured container or dispenser which contains a suitable propellant, *e.g.*, a gas such as carbon dioxide, or a nebulizer.

Systemic administration also can be by transmucosal or transdermal means. For transmucosal or transdermal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants generally are known in the art, and include, for example, for transmucosal administration, detergents and bile salts. Transmucosal administration can be accomplished through the use of nasal sprays or suppositories. For

transdermal administration, the active compounds typically are formulated into ointments, salves, gels, or creams as generally known in the art.

5 The active compounds may be prepared with carriers that will protect the compound against rapid elimination from the body, such as a controlled release formulation, including implants and microencapsulated delivery systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, and polylactic acid. Methods for preparation of such formulations will be apparent to those skilled in the art. Liposomal suspensions can also be used as pharmaceutically acceptable carriers. These can be prepared according to methods known to those skilled in the
10 art, for example, as described in U.S. Pat. No. 4,522,811.

Oral or parenteral compositions can be formulated in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form refers to physically discrete units suited as unitary dosages for the subject to be treated; each unit containing a predetermined quantity of active compound calculated to produce the desired therapeutic effect in association
15 with the required pharmaceutical carrier. The specification for the dosage unit forms of the invention are dictated by and directly dependent on the unique characteristics of the active compound and the particular therapeutic effect to be achieved, and the limitations inherent in the art of compounding such an active compound for the treatment of individuals. Furthermore, administration can be by periodic injections of a bolus, or can be made more continuous by
20 intravenous, intramuscular or intraperitoneal administration from an external reservoir (*e.g.*, an intravenous bag).

Where adhesion to a tissue surface is desired the composition can include the drug dispersed in a fibrinogen-thrombin composition or other bioadhesive. The compound then can be painted, sprayed or otherwise applied to the desired tissue surface. Alternatively, the drugs
25 can be formulated for parenteral or oral administration to humans or other mammals, for example, in therapeutically effective amounts, *e.g.*, amounts which provide appropriate concentrations of the drug to target tissue for a time sufficient to induce the desired effect.

Where the active compound is to be used as part of a transplant procedure, it can be provided to the living tissue or organ to be transplanted prior to removal of tissue or organ from
30 the donor. The compound can be provided to the donor host. Alternatively or, in addition, once removed from the donor, the organ or living tissue can be placed in a preservation solution

containing the active compound. In all cases, the active compound can be administered directly to the desired tissue, as by injection to the tissue, or it can be provided systemically, either by oral or parenteral administration, using any of the methods and formulations described herein and/or known in the art. Where the drug comprises part of a tissue or organ preservation solution, any commercially available preservation solution can be used to advantage. For example, useful solutions known in the art include Collins solution, Wisconsin solution, Belzer solution, Eurocollins solution and lactated Ringer's solution.

The active compound may be administered directly to a tissue locus by applying the compound to a medical device that is placed in contact with the tissue. For example, an active compound may be applied to a stent at the site of vascular injury. Stents can be prepared by any of the methods well known in the pharmaceutical art. *See, e.g.,* Fattori, R. and Piva, T., "Drug-Eluting Stents in Vascular Intervention," *Lancet*, **2003**, *361*, 247-249; Morice, M. C., "A New Era in the Treatment of Coronary Disease?" *European Heart Journal*, **2003**, *24*, 209-211; and Toutouzas, K. *et al.*, "Sirolimus-Eluting Stents: A Review of Experimental and Clinical Findings," *Z. Kardiol.*, **2002**, *91*(3), 49-57. The stent may be fabricated from stainless steel or another bio-compatible metal, or it may be made of a bio-compatible polymer. The active compound may be linked to the stent surface, embedded and released from polymer materials coated on the stent, or surrounded by and released through a carrier which coats or spans the stent. The stent may be used to administer single or multiple active compounds to tissues adjacent to the stent.

Active compound as identified or designed by the methods described herein can be administered to individuals to treat disorders (prophylactically or therapeutically). In conjunction with such treatment, pharmacogenomics (*i.e.*, the study of the relationship between an individual's genotype and that individual's response to a foreign compound or drug) may be considered. Differences in metabolism of therapeutics can lead to severe toxicity or therapeutic failure by altering the relation between dose and blood concentration of the pharmacologically active drug. Thus, a physician or clinician may consider applying knowledge obtained in relevant pharmacogenomics studies in determining whether to administer a drug as well as tailoring the dosage and/or therapeutic regimen of treatment with the drug.

In therapeutic use for treating, or combating, bacterial infections in mammals, the compounds or pharmaceutical compositions thereof will be administered orally, parenterally

and/or topically at a dosage to obtain and maintain a concentration, that is, an amount, or blood-level or tissue level of active component in the animal undergoing treatment which will be anti-microbially effective. The term "effective amount" is understood to mean that the compound of the invention is present in or on the recipient in an amount sufficient to elicit biological activity, for example, anti-microbial activity, anti-fungal activity, anti-viral activity, anti-parasitic activity, anti-proliferative activity, anti-inflammatory activity or ameliorating a symptom of a gastrointestinal motility disorder. Generally, an effective amount of dosage of active component will be in the range of from about 0.1 to about 100, more preferably from about 1.0 to about 50 mg/kg of body weight/day. The amount administered will also likely depend on such variables as the type and extent of disease or indication to be treated, the overall health status of the particular patient, the relative biological efficacy of the compound delivered, the formulation of the drug, the presence and types of excipients in the formulation, and the route of administration. Also, it is to be understood that the initial dosage administered may be increased beyond the above upper level in order to rapidly achieve the desired blood-level or tissue level, or the initial dosage may be smaller than the optimum and the daily dosage may be progressively increased during the course of treatment depending on the particular situation. If desired, the daily dose may also be divided into multiple doses for administration, for example, 2-4 four times per day.

In light of the foregoing, the specific examples presented below are illustrative only and are not intended to limit the scope of the invention. Other generic and specific configurations will be apparent to those persons skilled in the art.

6. Examples

Some of the abbreviations used in the following experimental details of the synthesis of the examples are defined below:

hr	=	hour(s)
min	=	minute(s)
mol	=	mole(s)
mmol	=	millimole(s)
M	=	molar
μM	=	micromolar
g	=	gram(s)

	μg	=	microgram(s)
	rt	=	room temperature
	L	=	liter(s)
	mL	=	milliliter(s)
5	Et_2O	=	diethyl ether
	THF	=	tetrahydrofuran
	DMSO	=	dimethyl sulfoxide
	EtOAc	=	ethyl acetate
	Et_3N	=	triethylamine
10	<i>i</i> -Pr ₂ NEt	=	diisopropylethylamine
	CH_2Cl_2	=	methylene chloride
	CHCl_3	=	chloroform
	CDCl_3	=	deuterated chloroform
	CCl_4	=	carbon tetrachloride
15	MeOH	=	methanol
	CD_3OD	=	deuterated methanol
	EtOH	=	ethanol
	DMF	=	dimethylformamide
	BOC	=	<i>t</i> -butoxycarbonyl
20	CBZ	=	benzyloxycarbonyl
	TBS	=	<i>t</i> -butyldimethylsilyl
	TBSCl	=	<i>t</i> -butyldimethylsilyl chloride
	TFA	=	trifluoroacetic acid
	DBU	=	diazabicycloundecene
25	TBDPSCI	=	<i>t</i> -butyldiphenylchlorosilane
	Hunig's Base	=	<i>N,N</i> -diisopropylethylamine
	DMAP	=	4-dimethylaminopyridine
	CuI	=	copper (I) iodide
	MsCl	=	methanesulfonyl chloride
30	NaN_3	=	sodium azide
	Na_2SO_4	=	sodium sulfate

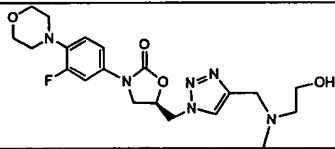
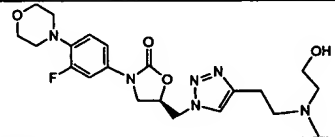
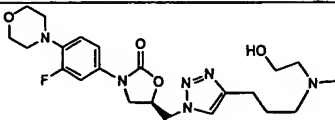
	NaHCO ₃	=	sodium bicarbonate
	NaOH	=	sodium hydroxide
	MgSO ₄	=	magnesium sulfate
	K ₂ CO ₃	=	potassium carbonate
5	KOH	=	potassium hydroxide
	NH ₄ OH	=	ammonium hydroxide
	NH ₄ Cl	=	ammonium chloride
	SiO ₂	=	silica
	Pd-C	=	palladium on carbon
10	Pd(dppf)Cl ₂	=	dichloro[1,1'-bis(diphenylphosphino)ferrocene] palladium (II)

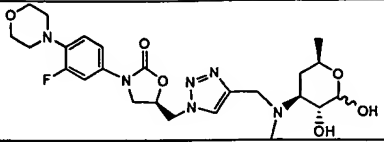
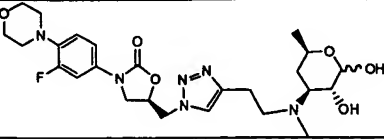
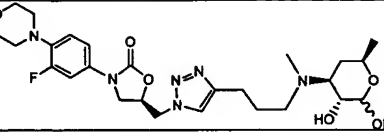
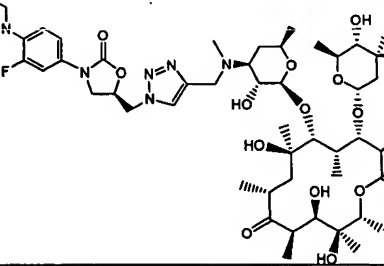
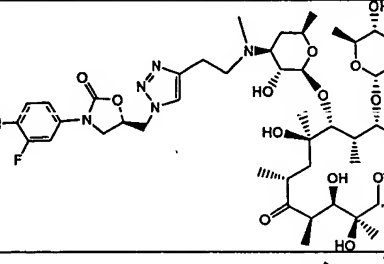
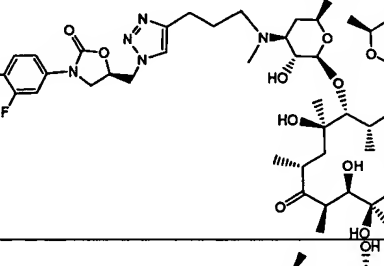
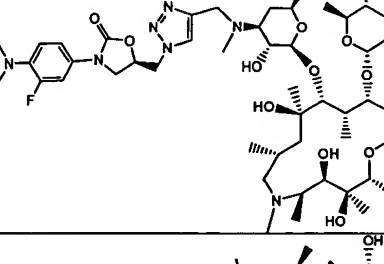
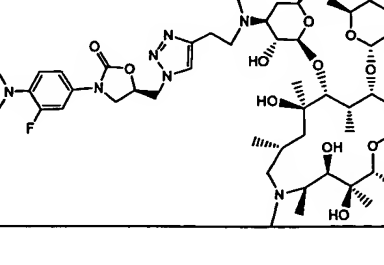
Nuclear magnetic resonance (NMR) spectra were obtained on a Bruker Avance 300 or Avance 500 spectrometer, or in some cases a GE-Nicolet 300 spectrometer. Common reaction solvents were either high performance liquid chromatography (HPLC) grade or American Chemical Society (ACS) grade, and anhydrous as obtained from the manufacturer unless otherwise noted. "Chromatography" or "purified by silica gel" refers to flash column chromatography using silica gel (EM Merck, Silica Gel 60, 230-400 mesh) unless otherwise noted.

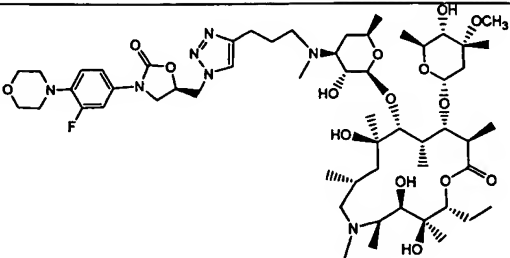
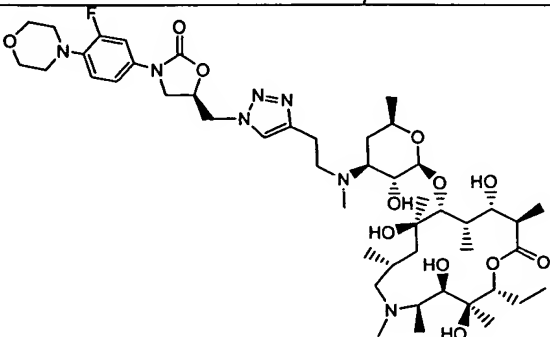
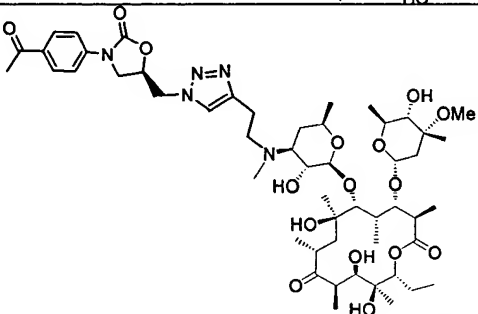
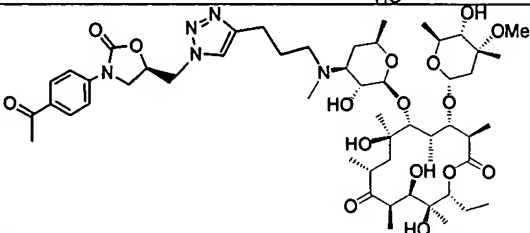
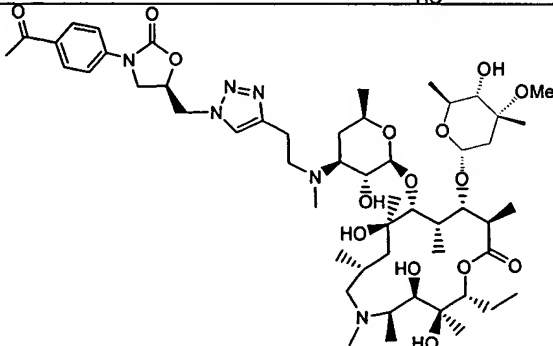
20 Example 1 - Exemplary Oxazolidinone Derivatives

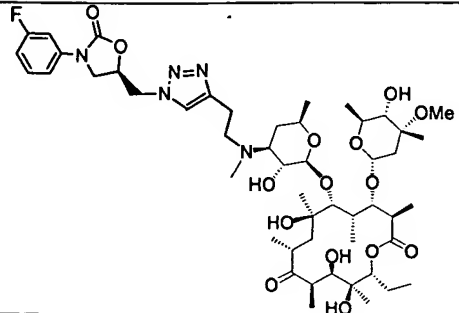
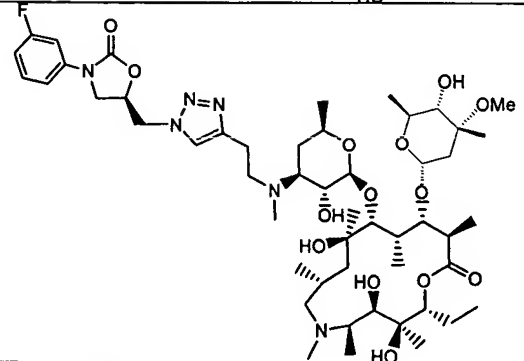
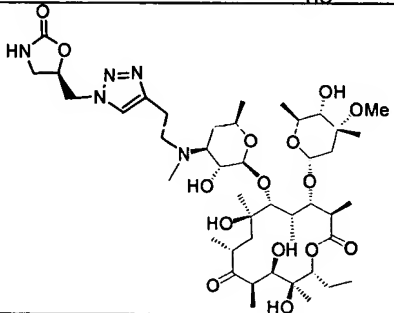
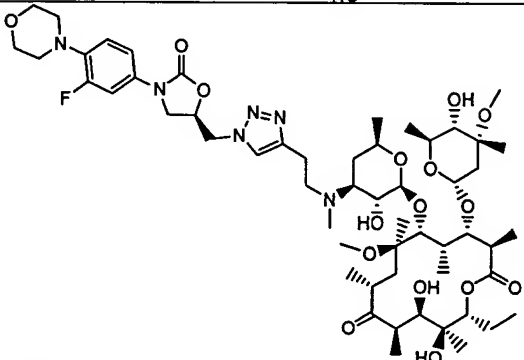
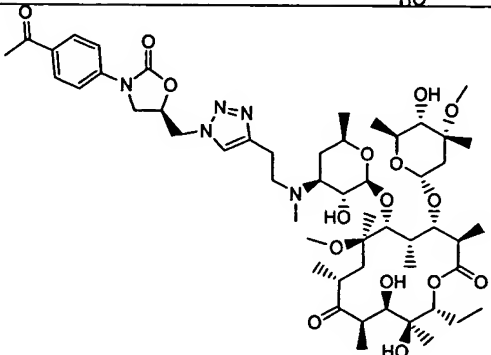
Exemplary compounds synthesized in accordance with the invention are listed in Table 2.

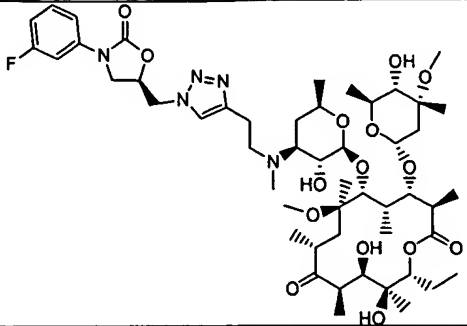
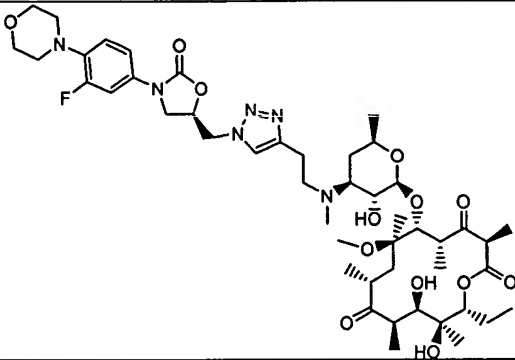
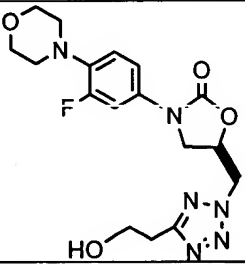
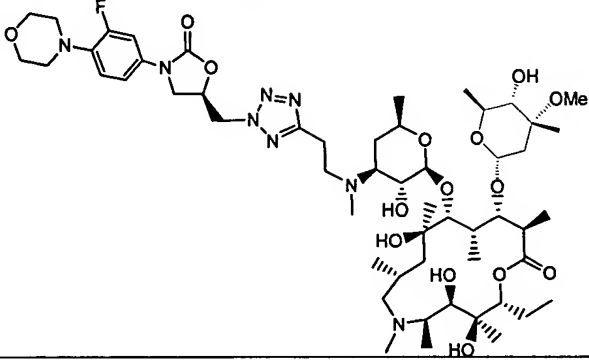
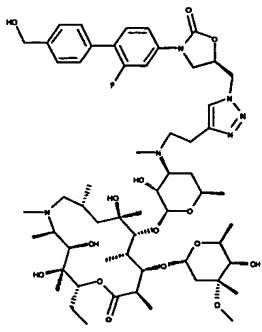
TABLE 2

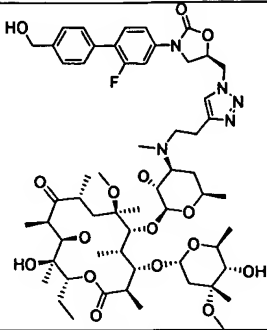
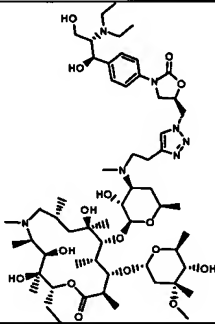
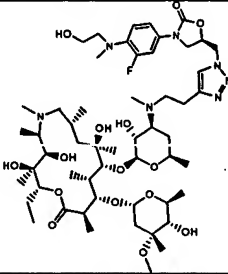
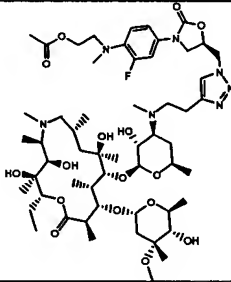
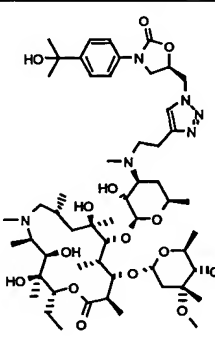
Compound Number	Structure
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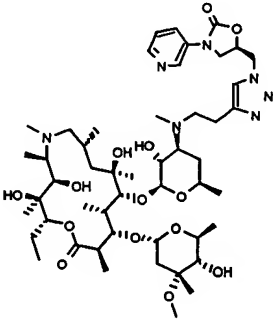
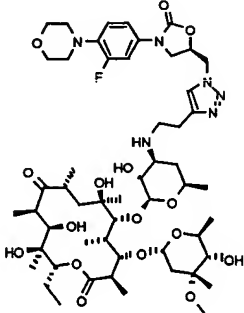
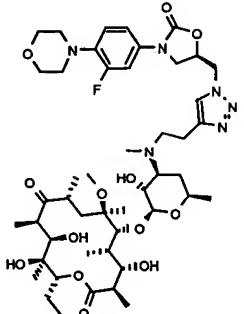
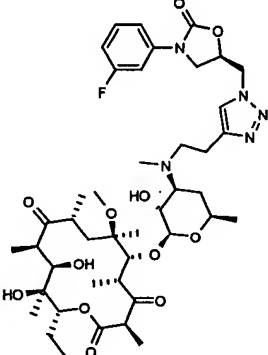
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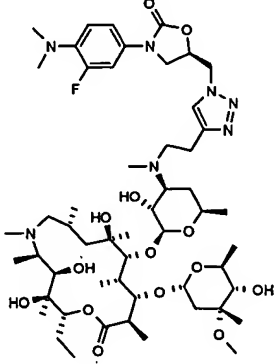
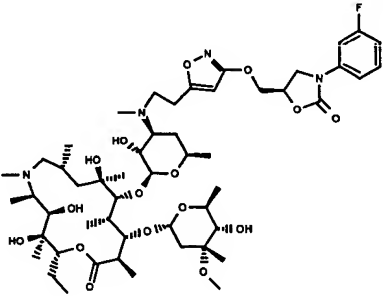
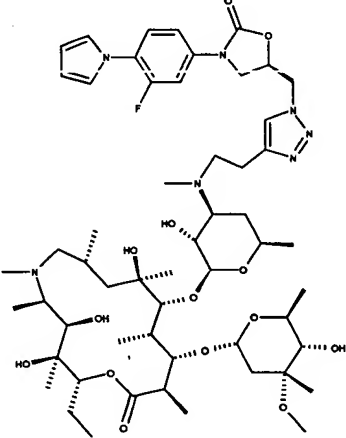
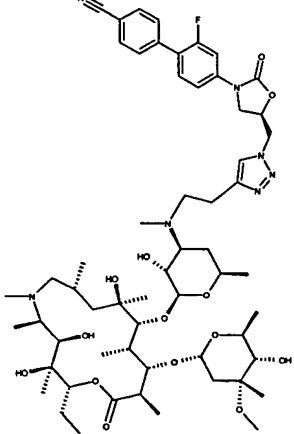
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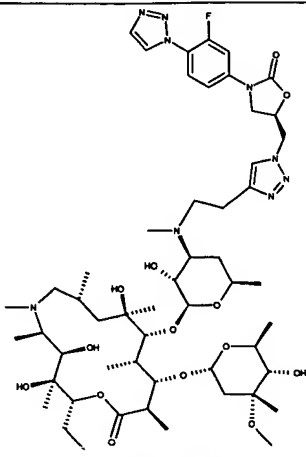
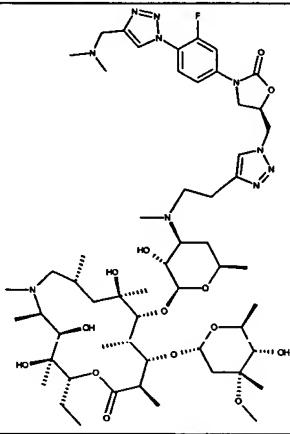
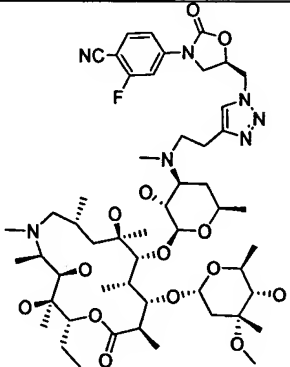
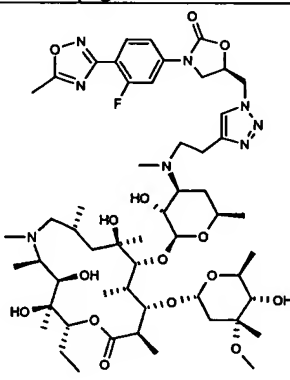
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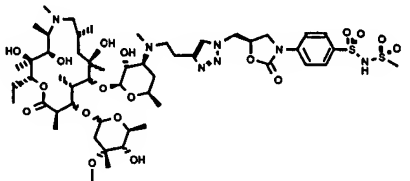
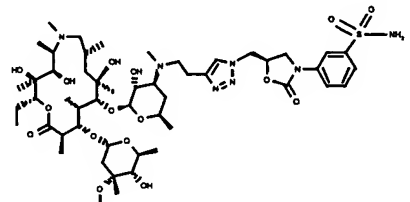
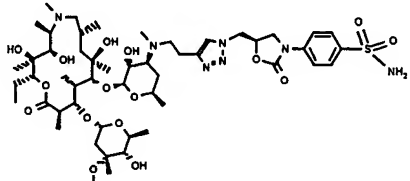
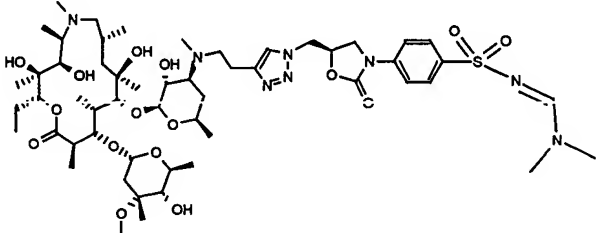
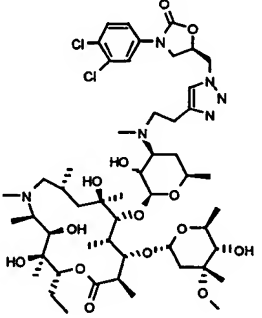
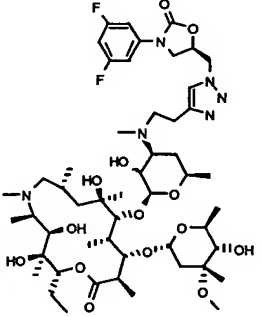
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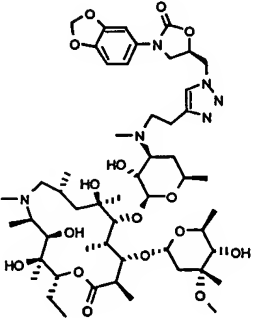
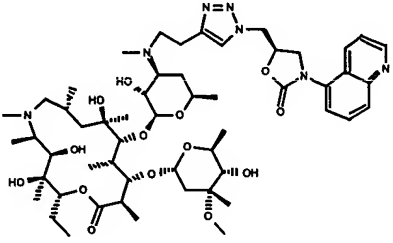
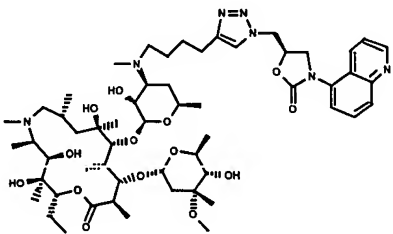
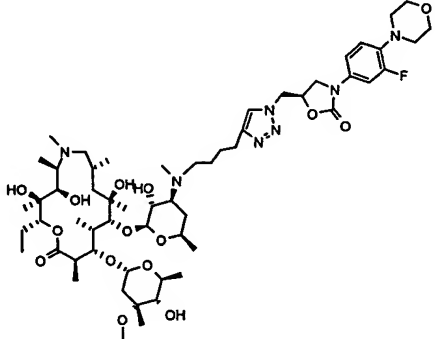
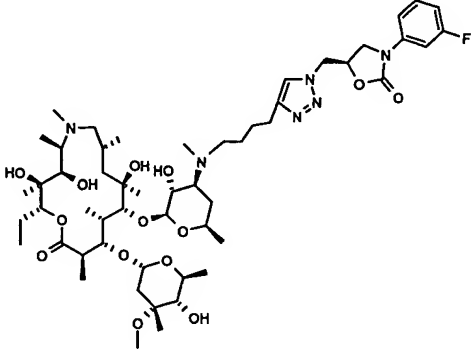
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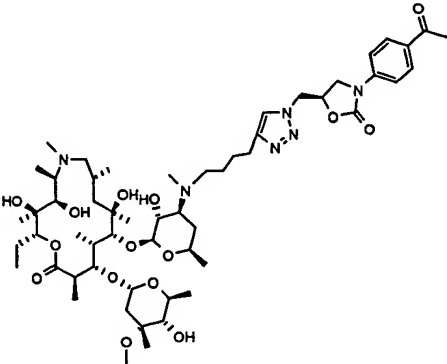
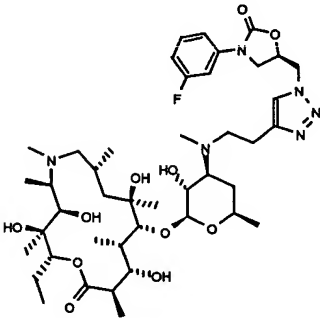
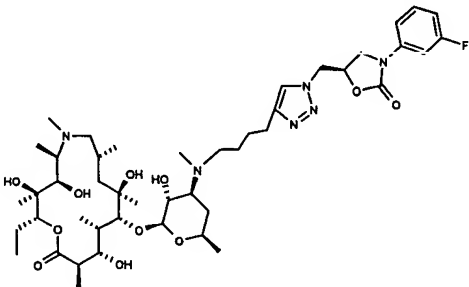
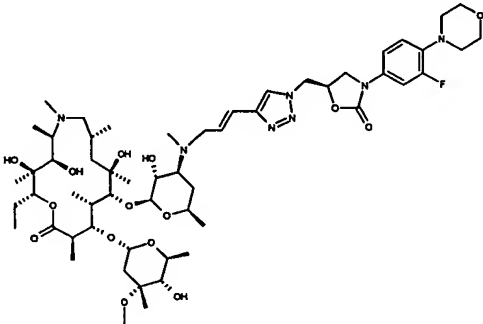
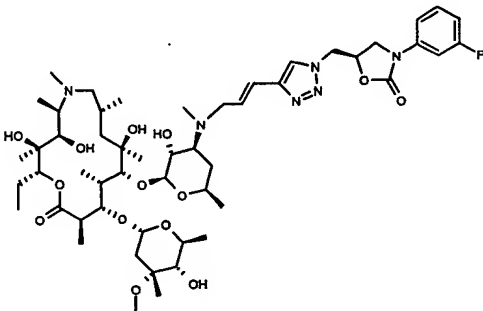
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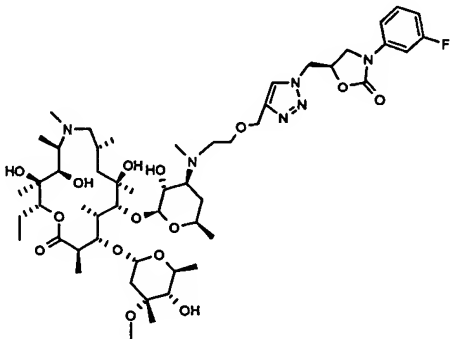
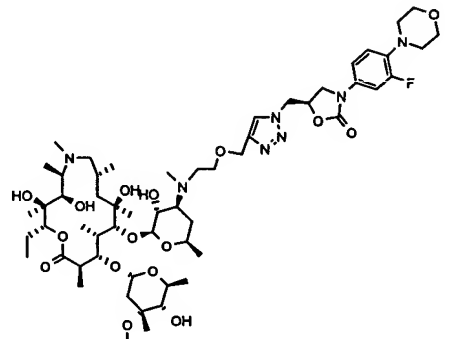
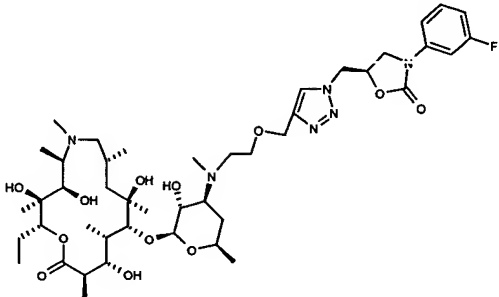
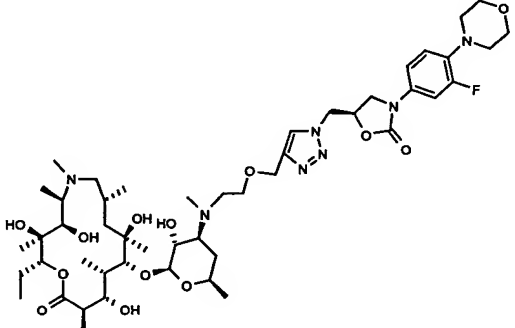
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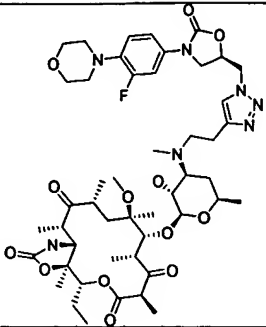
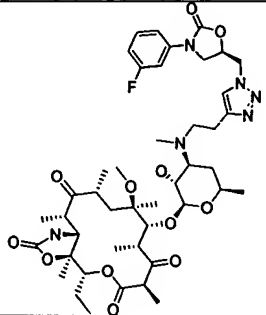
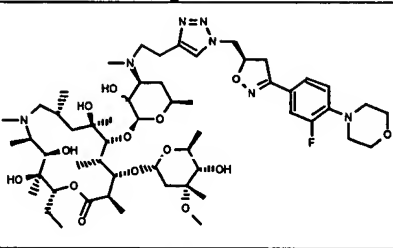
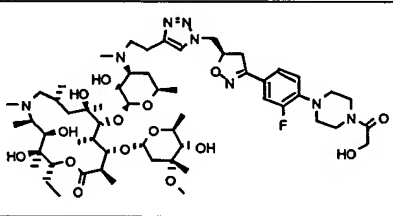
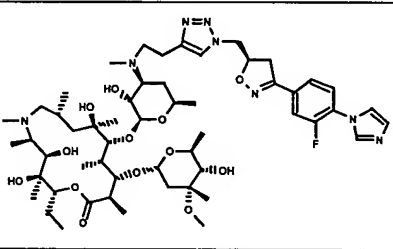
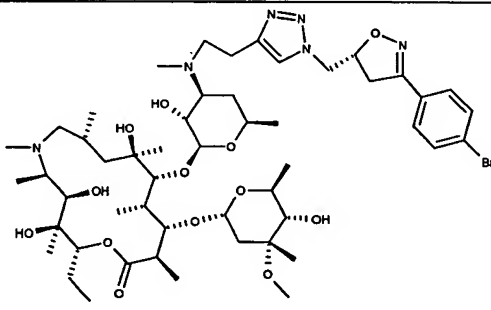
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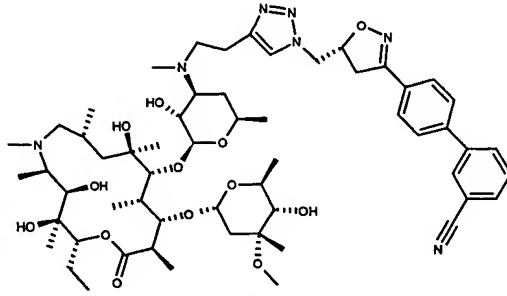
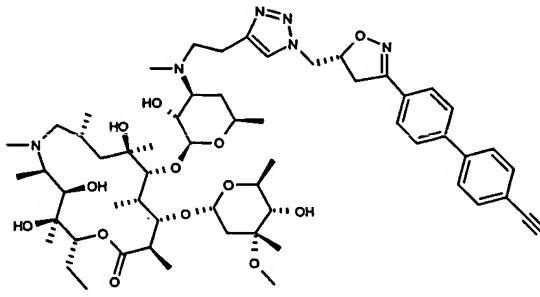
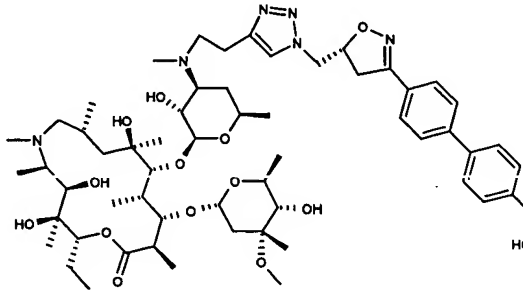
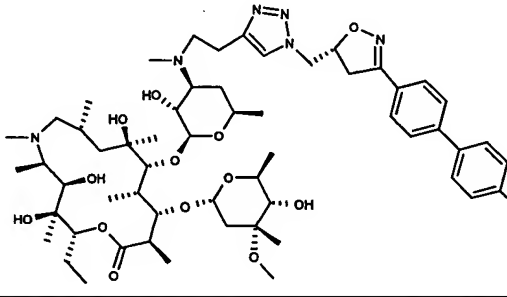
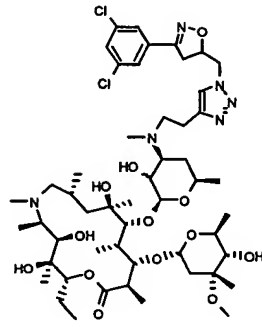
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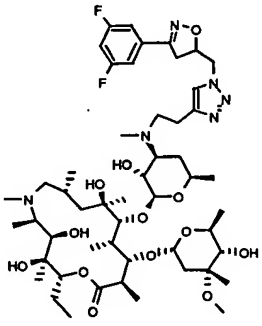
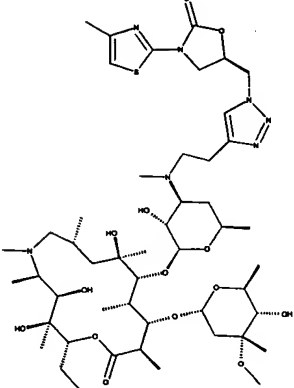
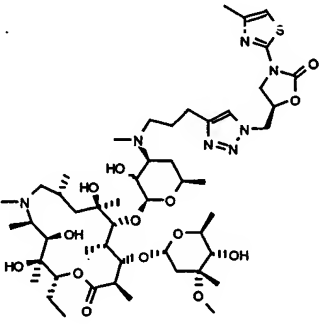
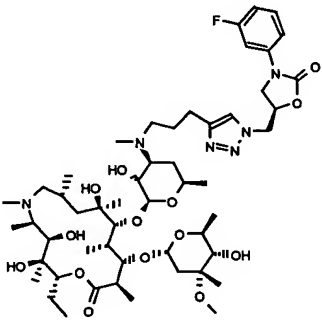
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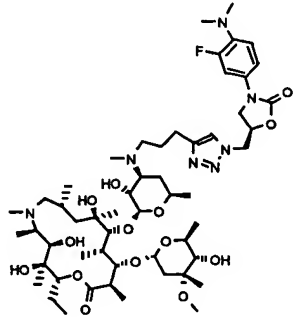
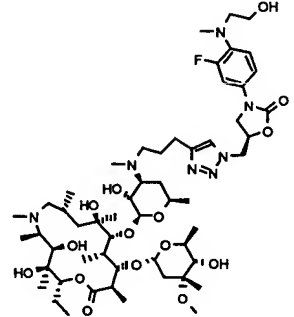
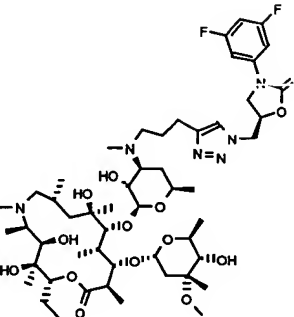
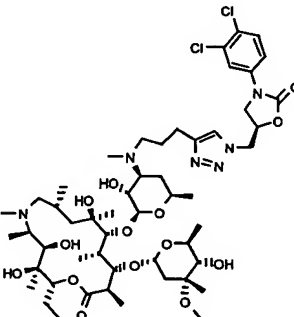
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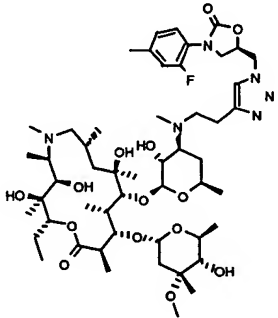
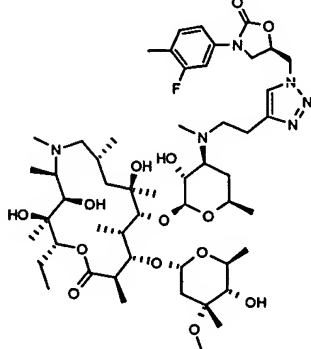
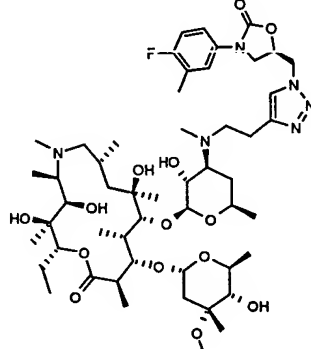
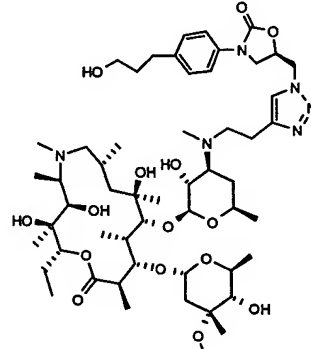
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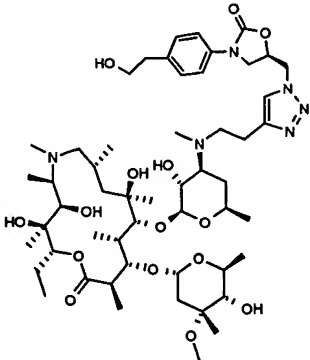
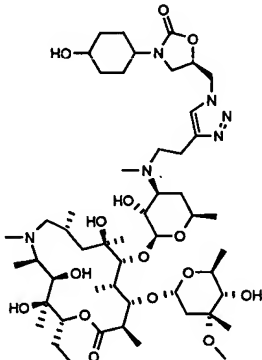
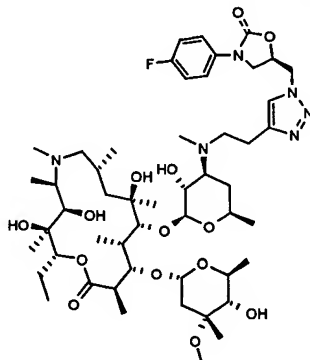
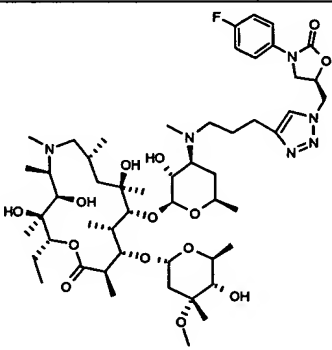
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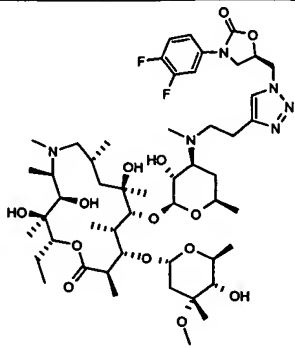
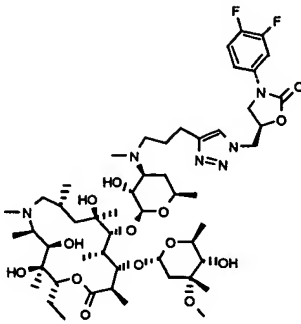
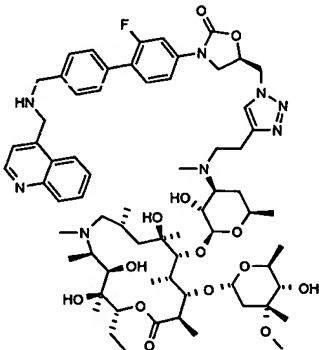
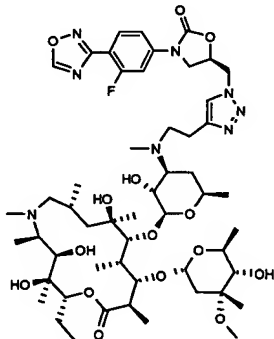
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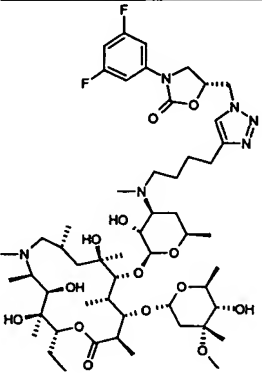
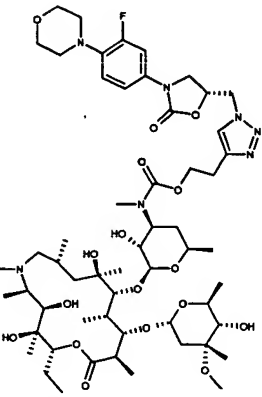
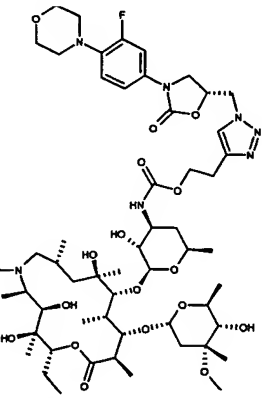
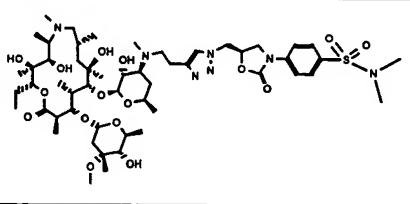
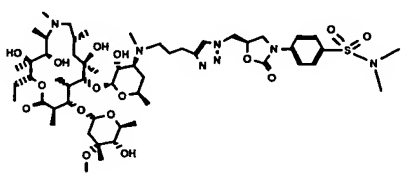
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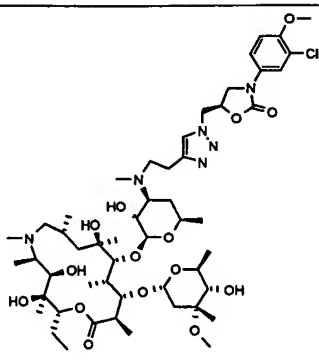
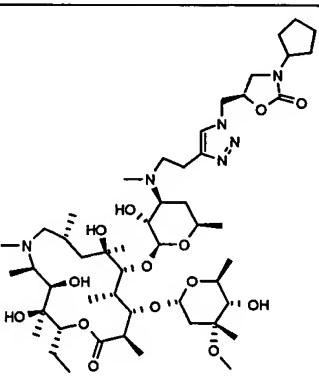
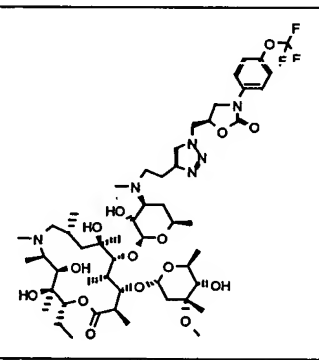
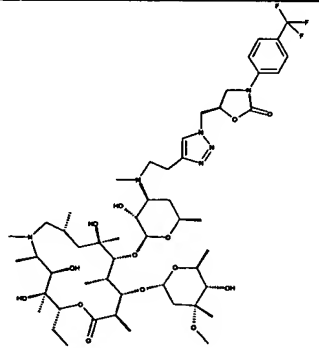
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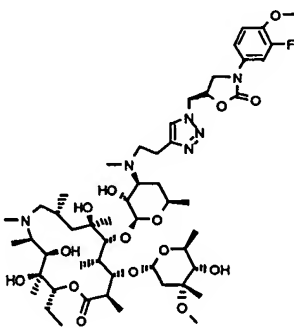
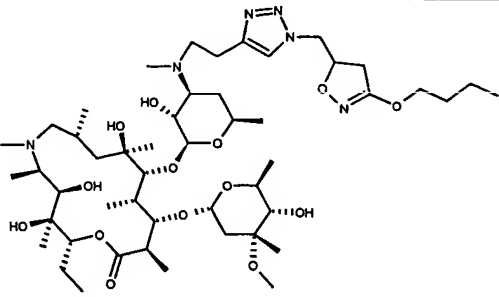
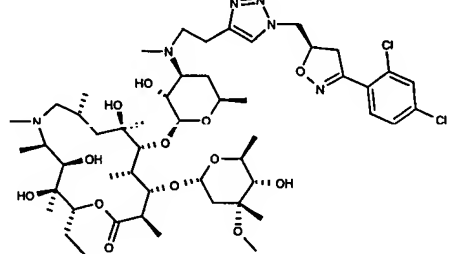
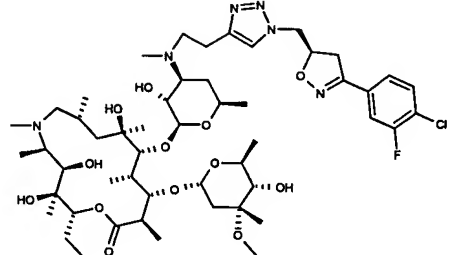
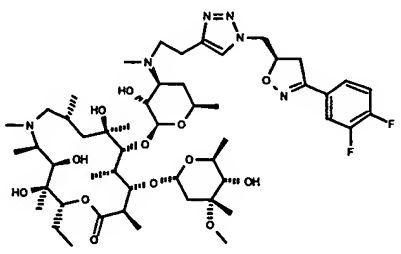
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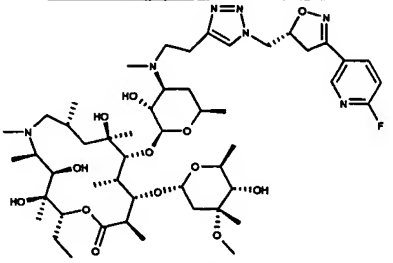
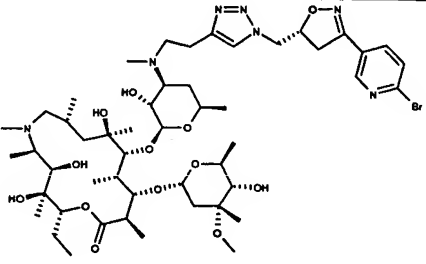
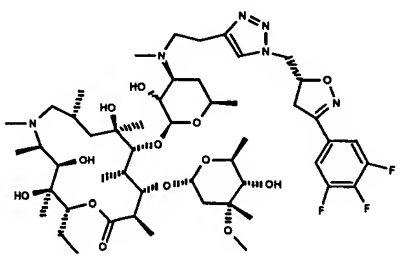
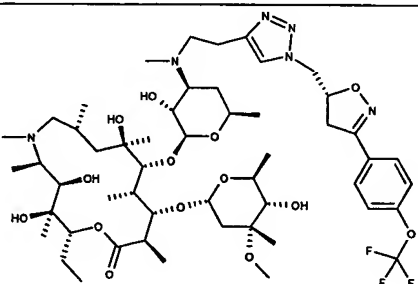
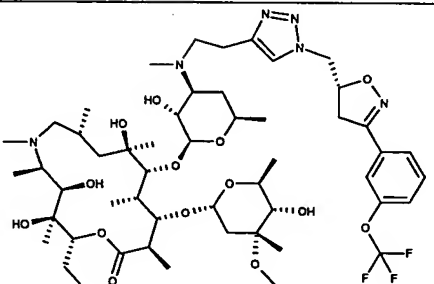
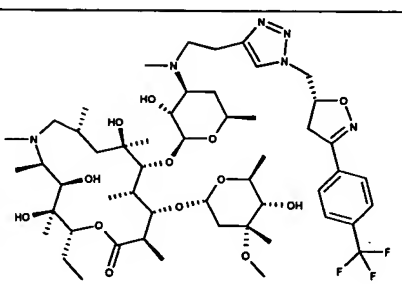
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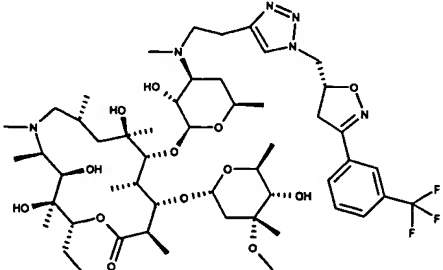
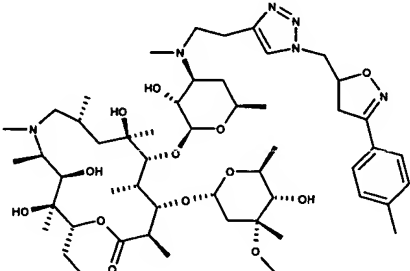
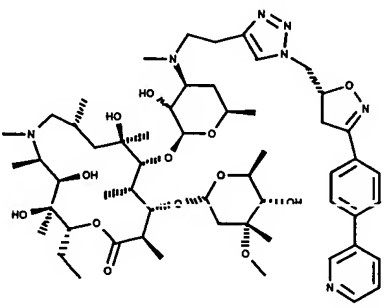
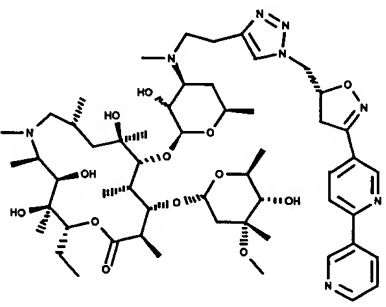
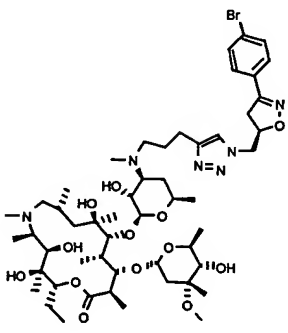
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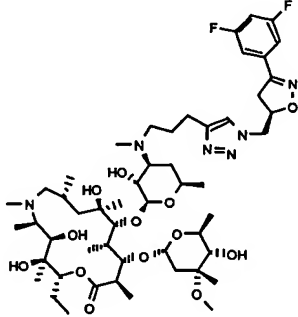
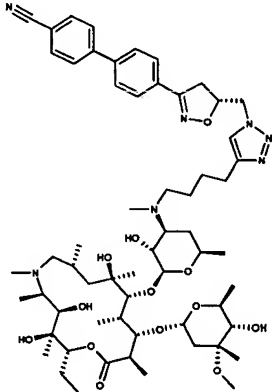
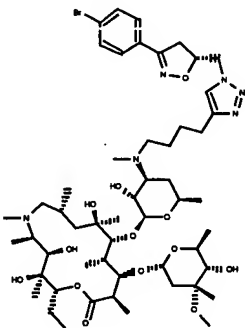
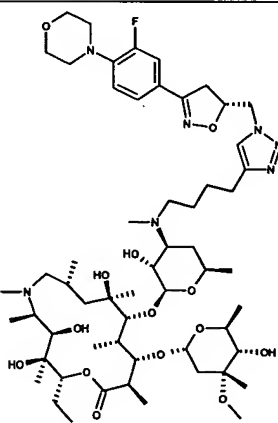
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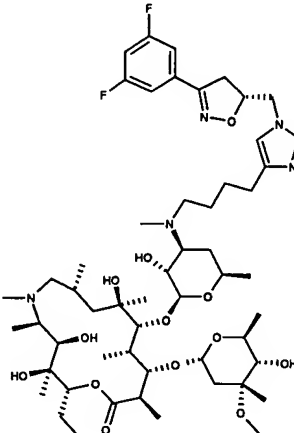
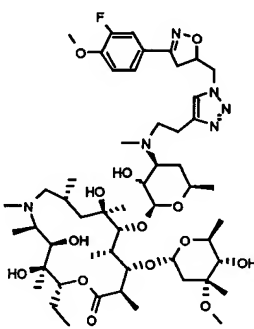
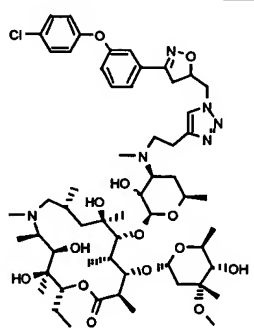
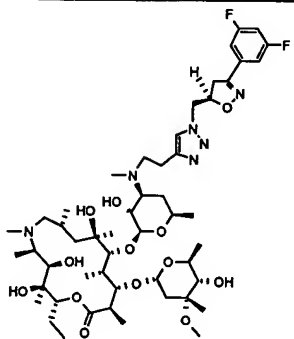
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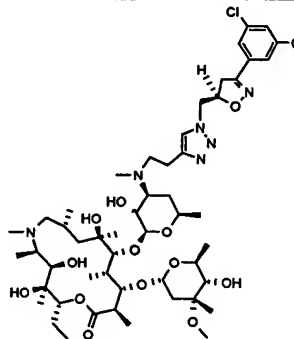
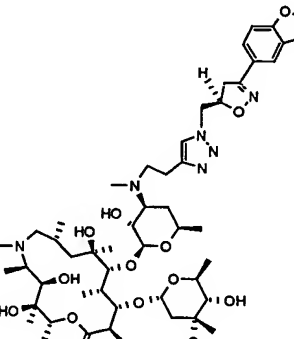
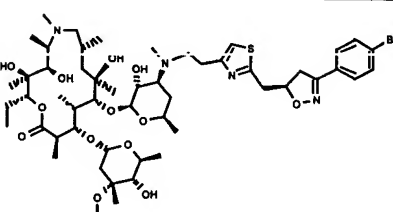
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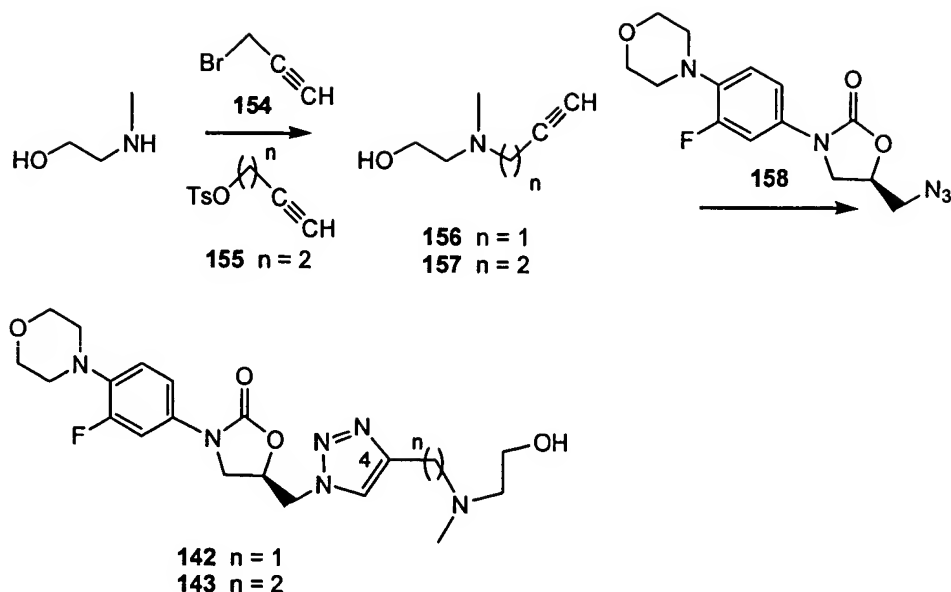
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Example 2 - Synthesis of Compounds 142 and 143

Scheme 28 below depicts the synthesis of compounds **142** and **143** using the chemistries previously exemplified. Briefly, 2-methylamino-ethanol was alkylated with propargyl bromide **154** and tosylate **155** to produce alkynes **156** and **157**, respectively. Alkynes **156** and **157** were heated in the presence of the azide intermediate **158** (Brickner, S.J. *et al.* (1996) J. MED. CHEM 39: 673) to produce compounds **142** and **143**, respectively.

Scheme 28



5 Synthesis of tosylate 155

3-Butyn-1-ol (1.8 g, 25 mmol) was dissolved in methylene chloride (CH₂Cl₂) (40 mL) and triethylamine (Et₃N) (4.18 mL, 30 mmol). The solution was stirred at 0°C followed by addition of p-toluenesulfonyl chloride (5.05 g, 26.25 mmol). The reaction was allowed to warm to room temperature over a period of 1 hour and stirring was continued overnight. Thin layer chromatography (TLC) analysis (hexanes/ethyl acetate (EtOAc) 6:1) after 20 hours of reaction showed a complete consumption of 3-butyn-1-ol. The precipitated triethylamine hydrochloride was filtered off and the filtrate washed with water (H₂O) (30 mL) and brine (30 mL). The organic layer was dried over sodium sulfate (Na₂SO₄) and the solvent evaporated away to give 155 as a light-yellow oil (5.45 g, 97%). The crude oil was used without further purification; however, it could be purified on a silica gel column, first eluting with 8% EtOAc in hexanes followed by 40% EtOAc in hexanes.

Synthesis of alkyne 157

A suspension of O-tosyl-3-butyn-1-ol (2.8 g, 12.5 mmol), 2-methylaminoethanol (0.93 mL, 11.4 mmol) and sodium bicarbonate (NaHCO₃) was heated at 50°C for 20 hours. NaHCO₃ was filtered, the solvent was evaporated, and the resulting residue was partitioned between H₂O

(30 mL) and EtOAc (30 mL). The layers were separated and the aqueous layer was back extracted with EtOAc (4 x 20 mL). The combined organic layer was dried over Na₂SO₄ and the solvent evaporated away to give an oily residue. The oily crude was purified on silica gel column eluting with 5:1 CH₂Cl₂/methanol (MeOH) to give compound **157** as an oil (0.54 g, 37%).

Synthesis of alkyne **156**

Alkyne **156** was made from 2-methylaminoethanol and propargyl bromide as described for alkyne **157** above.

Synthesis of triazole **142**

Azide **158** (0.15 g, 0.47 mmol) and alkyne **156** (0.212 g, 1.5 mmol) were dissolved in anhydrous tetrahydrofuran (THF) (10 mL) and Hunig's base (2 mL, 11.6 mmol). To this solution was added copper iodide (CuI) (0.136 g, 0.7 mmol) and the resulting suspension stirred at room temperature for 16 hours. TLC (chloroform (CHCl₃)/MeOH 10:1) showed a quantitative consumption of azide **158**. Methylene chloride (30 mL) was added, the suspension was filtered and solvent was evaporated from the filtrate. The residue was purified on silica gel eluting with 6-13% MeOH in CH₂Cl₂ to provide triazole **142** (0.11 g, 50.6%). Data for **142**: ¹H-NMR (500 MHz, CDCl₃) δ 7.78 (s, 1H), 7.30 (dd, *J* = 15, 3 Hz, 1H), 6.98 (dd, *J* = 9, 2 Hz, 1H), 6.88 (t, *J* = 10 Hz, 1H), 5.08 (m, 1H), 4.77 (m, 2H), 4.15 (t, *J* = 10 Hz, 1H), 3.94 (m, 1H), 3.85 (t, *J* = 5 Hz, 4H), 3.76 (bs, 2H), 3.60 (m, 2H), 3.03 (t, *J* = 4 Hz, 4H), 2.53 (m, 2H), 2.26 (s, 3H).

Synthesis of triazole **143**

Azide **158** (0.383 g, 1.2 mmol) and alkyne **157** (0.24 g, 1.9 mmol) were dissolved in anhydrous THF (12 mL) and Hunig's base (3 mL, 17.4 mmol). To this solution was added CuI (0.43 g, 2.2 mmol) and the resulting suspension was stirred at room temperature for 3 hours. TLC (CH₂Cl₂/MeOH 9:1) showed that the reaction was complete within 3 hours with no further consumption of azide **158** upon stirring overnight. Methylene chloride (50 mL) was added, the suspension was filtered and solvent was evaporated from the filtrate. The residue was purified on silica gel eluting with 10-20% MeOH in CH₂Cl₂ to provide triazole **143** (0.108 g, 20%). Data for **143**: ¹H-NMR (500 MHz, CDCl₃/CD₃OD) δ 7.78 (s, 1H), 7.33 (dd, *J* = 15, 3 Hz, 1H), 7.02

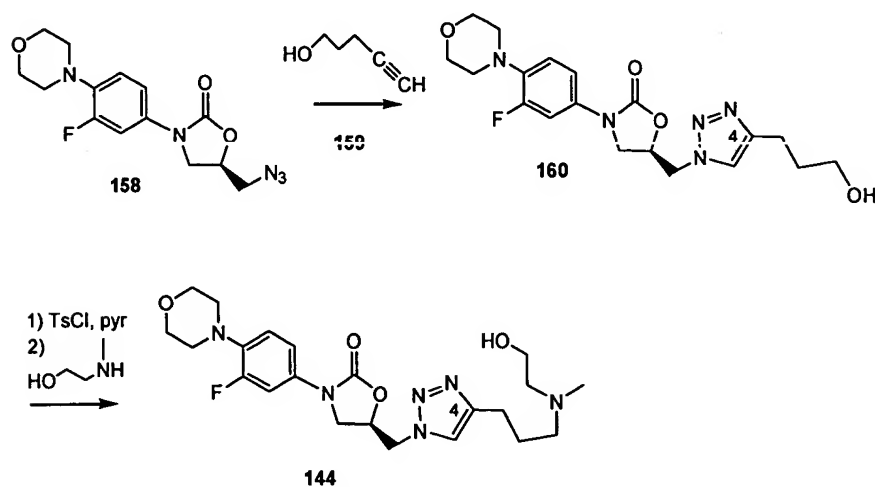
(dd, $J = 9, 2$ Hz, 1H), 6.95 (t, $J = 9$ Hz, 1H), 5.10 (m, 1H), 4.76 (m, 2H), 4.19 (t, $J = 9$ Hz, 1H), 3.93 (m, 1H), 3.87 (t, $J = 5$ Hz, 4H), 3.65 (m, 2H), 3.06 (t, $J = 5$ Hz, 4H), 2.90 (t, $J = 4$ Hz, 2H), 2.75 (t, $J = 5$ Hz, 2H), 2.62 (t, $J = 6$ Hz, 2H), 2.34 (s, 3H).

5 Example 3 - Synthesis of Compound 144

Scheme 29 below depicts the synthesis of compound **144** using the chemistries previously exemplified. Cycloaddition of azide **158** and alkyne **159** produced triazole **160**. Tosylation of the alcohol of triazole **160**, followed by alkylation with 2-methylamino-ethanol, produced 4-substituted triazole **144**.

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Scheme 29



15 Synthesis of alcohol 160

Azide **158** (0.15 g, 0.47 mmol) and 4-pentyn-1-ol (0.034 g, 0.39 mmol) were dissolved in anhydrous THF (10 mL) and Hunig's base (2 mL, 11.6 mmol). To this solution was added CuI (0.136 g, 0.7 mmol) and the resulting suspension was stirred at room temperature for 16 hours. TLC (CHCl₃/MeOH 10:1) showed a quantitative consumption of azide **158**. Methylene chloride (30 mL) was added, the suspension was filtered and solvent was evaporated from the filtrate. The residue was purified on silica gel eluting with 5-7% MeOH in CH₂Cl₂ to provide **160** (0.077 g, 48.7%).

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Synthesis of triazole 144

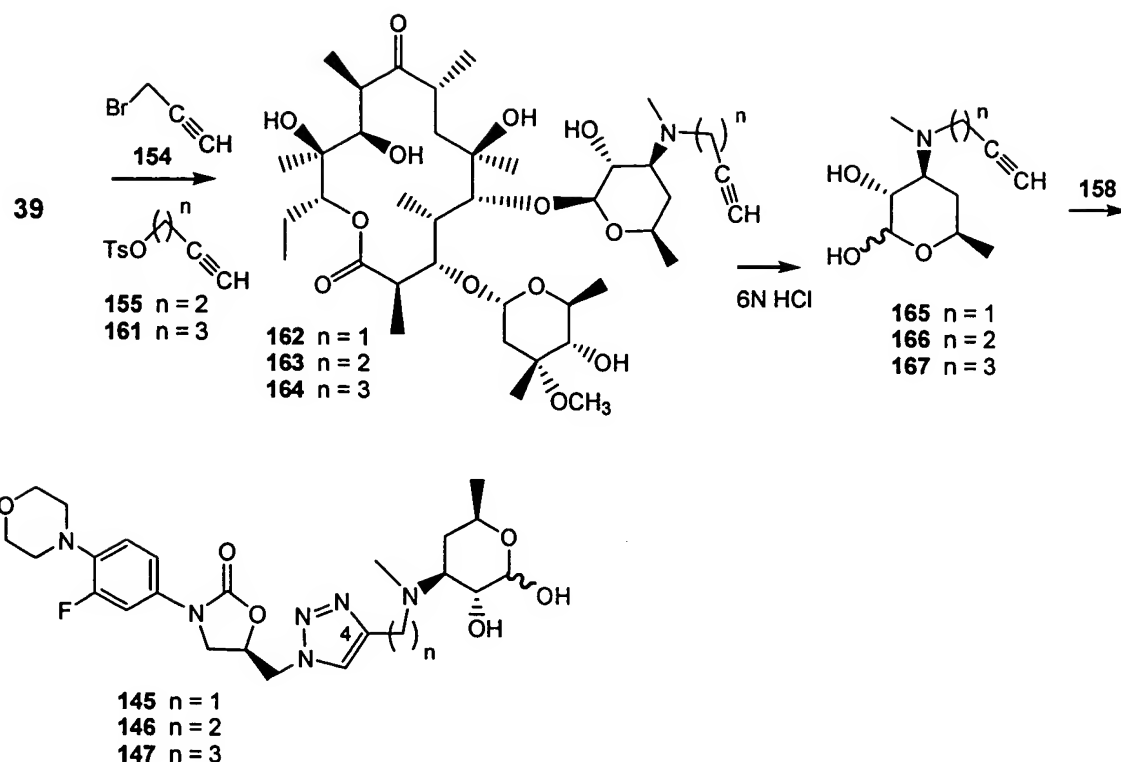
Compound **160** (0.072 g, 0.178 mmol) was dissolved in CH₂Cl₂ (2 mL) and Et₃N (0.09 mL, 0.63 mmol). To this solution was added p-toluenesulfonyl chloride (0.0366 g, 0.19 mmol) and stirring continued at room temperature for 20 hours during which a quantitative consumption of compound **160** was noticed by TLC (CH₂Cl₂/MeOH 9:1). The reaction was quenched with 10:1 H₂O/THF within 30 minutes and then partitioned between 10% NaHCO₃ (20 mL) and CH₂Cl₂ (20 mL). The two layers were separated; and the organic layer washed with saturated brine (3 x 15 mL) and dried over Na₂SO₄. Solvent was evaporated to give an oily residue.

The crude product above was dissolved in THF (3 mL) and Hunig's base (0.31 mL, 1.8 mmol). To this solution was added 2-(methylamino)ethanol (0.037 mL, 0.45 mmol) and stirring was continued at room temperature for 20 hours. The reaction was partitioned between 5% MeOH in CH₂Cl₂ (30 mL) and saturated brine (20 mL). The two layers were separated and the resulting organic layer was washed with saturated brine (2 x 20 mL), dried over Na₂SO₄ and the solvent was evaporated. The crude product was purified on silica gel eluting with 15-35% MeOH in CH₂Cl₂ to CH₂Cl₂/MeOH/ammonium hydroxide (NH₄OH) 3:1:0.05 to provide compound **144** (0.041 g, 50%). Data for **144**: ¹H-NMR (500 MHz, CDCl₃/CD₃OD) δ 7.77 (s, 1H), 7.34 (dd, *J* = 15, 3 Hz, 1H), 7.04 (dd, *J* = 9, 2.5 Hz, 1H), 6.98 (t, *J* = 9 Hz, 1H), 5.12 (m, 1H), 4.77 (m, 2H), 4.20 (t, *J* = 9 Hz, 1H), 3.96 (m, 1H), 3.86 (t, *J* = 5 Hz, 4H), 3.63 (m, 2H), 3.05 (t, *J* = 5 Hz, 4H), 2.71 (t, *J* = 6 Hz, 2H), 2.52 (t, *J* = 6 Hz, 2H), 2.42 (t, *J* = 8 Hz, 2H), 2.26 (s, 3H), 1.83 (m, 2H).

Example 4 - Synthesis of Compounds 145-147

Scheme 30 below depicts the synthesis of compounds **145-147** using chemistries previously exemplified. Des-methyl erythromycin amine **39** was alkylated with propargyl bromide **154** or the tosylates **155** and **161** to produce alkynes **162**, **163** and **164**, respectively. Hydrolysis of alkynes **162**, **163** and **164** produces alkynes **165**, **166** and **167**, respectively, which were then used in a cycloaddition reaction with azide **158** to produce the 4-substituted triazole compounds **145**, **146** and **147**, respectively.

Scheme 30



Synthesis of tosylate 161

Tosylate **161** was made from 4-pentyn-1-ol using the same protocol described for the synthesis of tosylate **155** above.

Synthesis of alkyne 165

Alkyne **162** (800 mg) was stirred with 6N hydrochloric acid (HCl) overnight at ambient temperature and heated to 100°C for 2 hours. The dark solution was cooled to room temperature and extracted with CH₂Cl₂ (3 x 8 mL) and ethyl ether (Et₂O) (3 x 8 mL). The aqueous phase was concentrated to obtain a foamy solid, which was redissolved in water (8 mL) and neutralized with NaHCO₃. The solution was extracted with EtOAc (3 x 10 mL), dried with Na₂SO₄, concentrated and purified by flash chromatography (silica gel, 5% MeOH-CHCl₃) to give the alkyne **165** (85 mg, 40%) as a mixture of anomers.

Synthesis of alkyne 166 and 167

The same procedure used for the synthesis of alkyne **165** from **162** was used to synthesize alkyne **166** from **163**, and alkyne **167** from **164**. The alkynes **166** and **167** were used in subsequent chemistry without further purification.

Synthesis of triazole 145

To a solution of alkyne **165** (80 mg, 0.0402 mmol), azide **158** (155 mg, 0.482 mmol), and Hunig's base (2.1 mL, 12.06 mmol) in THF (5 mL) was added CuI (156 mg, 0.804 mmol) and the mixture was stirred overnight at ambient temperature. The reaction mixture was diluted with 10% MeOH-CHCl₃ (50 mL), washed with brine (2 x 50 mL), dried with Na₂SO₄, and concentrated under reduced pressure. The crude mixture was purified by flash chromatography (silica gel, 10% MeOH-CHCl₃) to give compound **145** (80 mg, 40%). Data for **145**: ¹H-NMR (500 MHz, CDCl₃; partial structure) δ 7.72 (s, 1H), 7.28 (d, 1H), 6.95-6.84 (m, 2H, m).

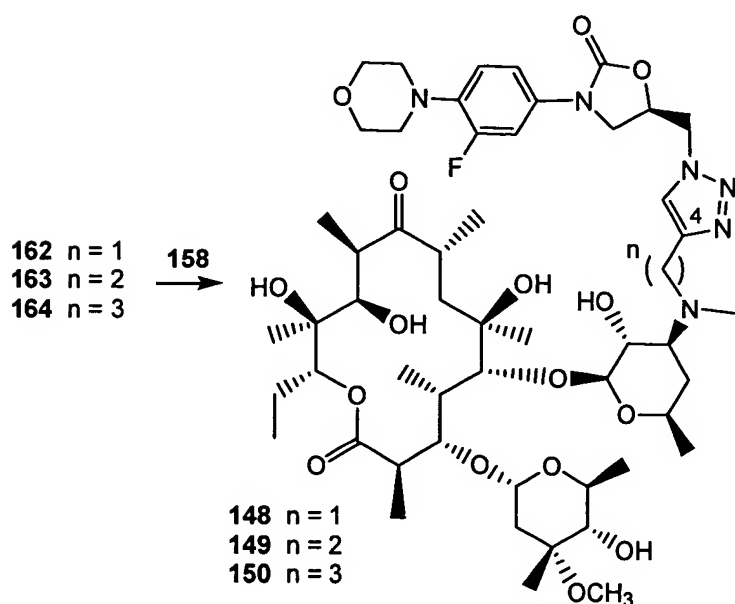
Synthesis of triazoles 146 and 147

The same procedure used for the synthesis of triazole **145** from **165** was used to synthesize triazole **146** from alkyne **166**, and triazole **147** from alkyne **167**.

Example 5 - Synthesis of Compounds 148-150

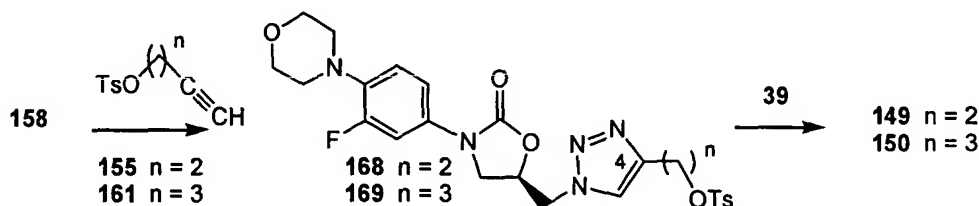
Scheme 31 below depicts the synthesis of compounds **148-150** using one exemplary method. Alkynes **162**, **163** and **164** were reacted with azide **158** to produce a mixture of the 4-substituted triazoles **148**, **149**, and **150**, respectively.

Scheme 31



Scheme 32 below depicts the synthesis of compounds **149** and **150** using an alternative exemplary method. Azide **158** was reacted with tosylates **155** and **161** to produce triazole tosylates **168** and **169**, respectively. The reaction of compounds **168** and **169** with amine **39** produced compounds **149** and **150**, respectively.

Scheme 32



Synthesis of amine **39**

Compound **39** was made from erythromycin A employing the procedure described in U.S. Patent No. 3,725,385.

Synthesis of alkyne **163**

A mixture of des(N-methyl)erythromycin **39** (1.0 g, 1.4 mmol) and tosylate **155** (1.25 g, 5.6 mmol) in anhydrous THF (15 mL) and Hunig's base (2.2 mL, 11.9 mmol) was kept stirring at 55°C for 48 hours. The reaction was poured into CH₂Cl₂ (50 mL), extracted with 2% aqueous NH₄OH (3 x 30 mL) and saturated brine (1 x 30 mL). The organic layer was dried over Na₂SO₄ and the solvent was evaporated away. The crude was purified on silica gel column eluting with CH₂Cl₂/MeOH 10:1 to give **163** (0.35 g, 32%).

Synthesis of alkyne **164**

Alkyne **164** was made from des(N-methyl)erythromycin **39** and tosylate **161** using the same procedure described for alkyne **163**.

Synthesis of alkyne **162**

Alkyne **162** was made from des(N-methyl)erythromycin **39** and propargyl bromide using the same procedure described for alkyne **163**.

Synthesis of tosylate 168

Azide **158** (1.5 g, 4.7 mmol) and tosylate **155** (0.875 g, 3.9 mmol) were dissolved in anhydrous THF (25 mL) and Hunig's base (10 mL, 57.4 mmol). To this solution was added CuI (1.36 g, 7.0 mmol) and the resulting suspension was stirred at room temperature for 2 hours.

- 5 TLC (CHCl₃/MeOH 10:1) showed a quantitative consumption of azide **158**. The reaction was poured into CH₂Cl₂ (60 mL), extracted with saturated NaHCO₃ (3 x 30 mL) and saturated brine (2 x 30 mL). The organic layer was dried over Na₂SO₄ and the solvent was evaporated away. The crude was purified on silica gel column eluting with 0-3% MeOH in CH₂Cl₂ to give **168** (1.34 g, 63%).

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Synthesis of triazole 149

- Method A: Alkyne **163** (0.80 g, 1.036 mmol) and azide **158** (0.50 g, 1.6 mmol) were dissolved in anhydrous THF (10 mL) and Hunig's base (2.2 mL, 11.6 mmol). To this solution was added CuI (0.403 g, 2.07 mmol) and the resulting suspension stirred at room temperature for 15 2 hours. CH₂Cl₂ (60 mL) was added, the solution was extracted with saturated NaHCO₃ (3 x 30 mL), NH₄Cl (3 x 30 mL) and saturated brine (30 mL). The organic layer was dried over Na₂SO₄ and the solvent was evaporated. The crude was purified on silica gel eluting with CH₂Cl₂/MeOH 15:1 to 10:1 to provide triazole **149** (0.91 g, 80%).

- Method B: A mixture of des(N-methyl)erythromycin **39** (0.25 g, 0.342 mmol) and 20 tosylate **168** (0.28 g, 0.51 mmol) in anhydrous THF (5 mL) and Hunig's base (0.65 mL, 3.51 mmol) was stirred at 55°C for 48 hours. The reaction was poured into CH₂Cl₂ (30 mL), extracted with saturated NaHCO₃ (3 x 20 mL) and saturated brine (1 X 20 mL). The organic layer was dried over Na₂SO₄ and the solvent evaporated. The crude product was purified on silica gel column eluting with CH₂Cl₂/MeOH 15:1 to 10:1 to give triazole **149** (0.151 g, 40%).

- 25 Data for **149**: ¹H-NMR, partial, (500 MHz, CDCl₃) δ 7.60 (s, 1H), 7.29 (dd, *J* = 14, 3 Hz, 1H), 6.95 (dd, *J* = 10, 3 Hz, 1H), 6.86 (t, *J* = 9 Hz, 1H), 5.00 (m, 2H), 4.85 (d, *J* = 5 Hz, 1H), 4.67 (m, 2H), 4.37 (d, *J* = 7 Hz, 1H), 4.08 (t, *J* = 10 Hz, 1H), 3.52 (d, *J* = 8 Hz, 1H), 3.44 (m, 1H), 2.66 (m, 2H), 0.82 (t, *J* = 8 Hz, 3H).

Synthesis of triazole 148

Triazole **148** was made from alkyne **162** and azide **158** using method A as described for triazole **149**.

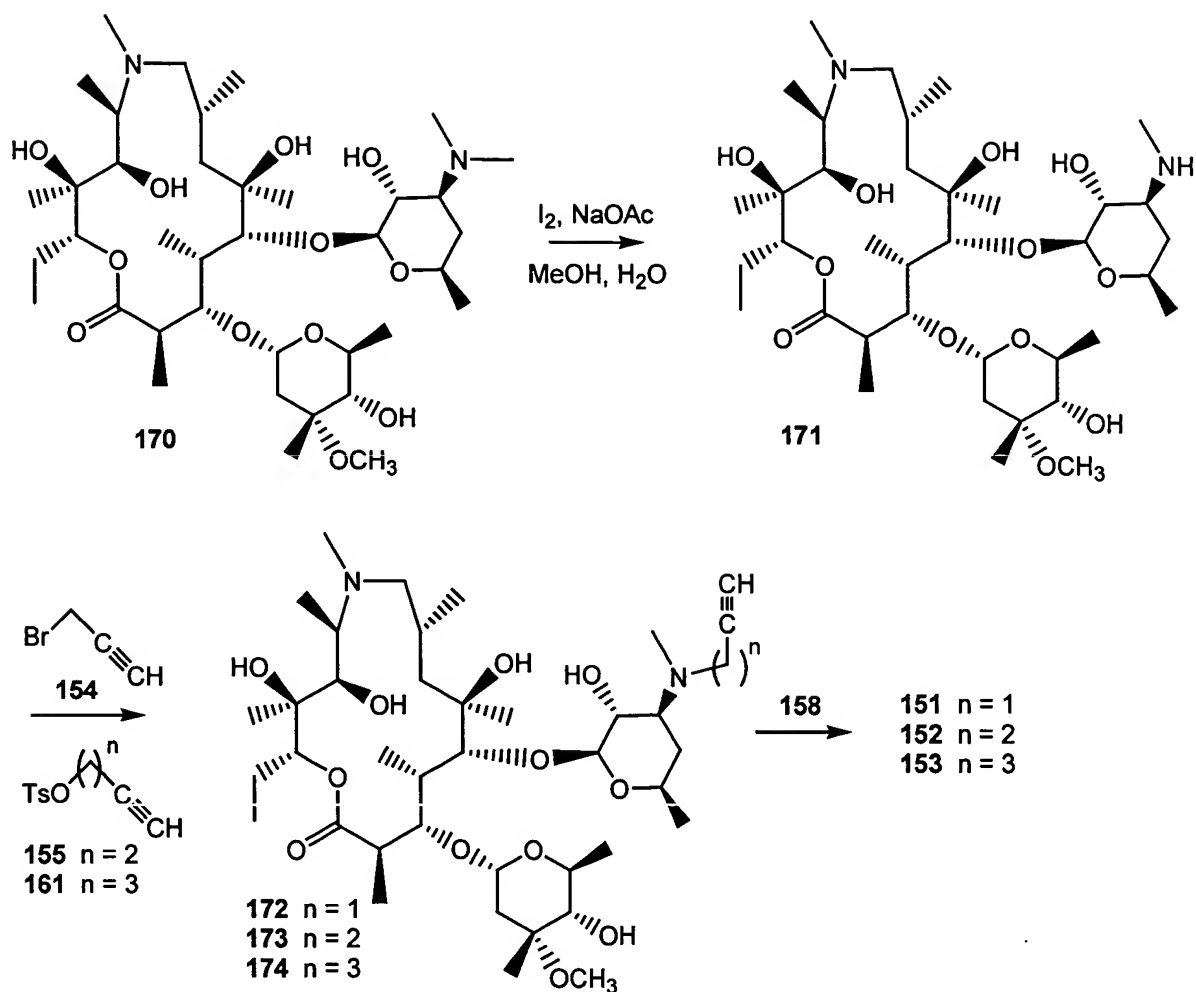
5 Synthesis of triazole 150

Triazole **150** was made from alkyne **164** and azide **158** using both methods A and B described for triazole **149**. Data for **150**: ¹H-NMR, partial, (500 MHz, CDCl₃) δ 7.49 (s, 1H), 7.26 (dd, *J* = 15, 3 Hz, 1H), 6.91 (dd, *J* = 10, 3 Hz, 1H), 6.84 (t, *J* = 9 Hz, 1H), 5.00 (m, 2H), 4.85 (d, *J* = 5 Hz, 1H), 4.67 (m, 2H), 4.38 (d, *J* = 8 Hz, 1H), 4.07 (t, *J* = 10 Hz, 1H), 3.52 (d, *J* = 8 Hz, 1H), 3.44 (m, 1H), 2.69 (m, 2H), 0.78 (t, *J* = 8 Hz, 3H).

Example 6 - Synthesis of Compounds 151-153

Scheme 33 below depicts the synthesis of compounds **151-153** using the chemistries previously exemplified. Demethylation of azithromycin **170** selectively produced amine **171**.
15 Amine **171** was alkylated with bromide **154** and tosylates **155** and **161** to produce alkynes **172**, **173** and **174**, respectively. Cycloaddition of alkynes **172**, **173** and **174** with azide **158** produced compounds **151**, **152** and **153**, respectively.

Scheme 33



Synthesis of des(N-methyl)azithromycin **171**

Azithromycin **170** (0.80 g, 1.02 mmol) and sodium acetate (NaOAc) (0.712 g, 8.06 mmol) were dissolved in 80% aqueous MeOH (25 mL). The solution was kept at 50°C followed by addition of iodine (I_2) (0.272 g, 1.07 mmol) in three batches within 3 minutes. The reaction was maintained at a pH between 8 – 9 by adding 1N sodium hydroxide (NaOH) (1 mL) at 10 min and 45 minute intervals. The solution turned colorless within 45 minutes, however, stirring was continued for 2 hours. TLC (CH_2Cl_2 /MeOH/ NH_4OH 10:1:0.05) after 2 hours showed a single major product (R_f = 0.66). The reaction was cooled to room temperature, poured into H_2O (75 mL) containing NH_4OH (1.5 mL) and extracted with $CHCl_3$ (3 x 30 mL). The combined organic layer was washed with H_2O (30 mL) containing NH_4OH (1.5 mL), dried over Na_2SO_4 and the solvent evaporated to give a white residue. The crude was purified on silica gel column eluting with CH_2Cl_2 /MeOH/ NH_4OH 18:1:0.05 to 10:1:0.05 to provide amine **171** (0.41 g, 55%).

Synthesis of alkyne 172

Alkyne 172 was made from des(N-methyl)azithromycin 171 and propargyl bromide using the same procedure described for the synthesis of compound 163.

5 Synthesis of alkyne 173

Alkyne 173 was made from des (N-methyl)azithromycin 171 and tosylate 155 using the same procedure described for the synthesis of compound 163.

Synthesis of triazole 151

10 Triazole 151 was made from alkyne 172 and azide 158 using method A as described for the synthesis of compound 149.

Synthesis of triazole 152

15 Triazole 152 was made from alkyne 173 and azide 158 using method A as described for the synthesis of compound 149. Data for 152: ¹H-NMR (300 MHz, CDCl₃, partial): δ 7.63 (s, 1H), 7.34 (dd, *J* = 14, 2 Hz, 1H), 6.98 (dd, *J* = 9, 2 Hz, 1H), 6.90 (t, *J* = 9 Hz, 1H), 5.11 (d, *J* = 4 Hz, 1H), 4.96 (m, 1H), 4.71 (m, 3H), 4.44 (d, *J* = 7 Hz, 1H), 4.30 (d, *J* = 2 Hz, 1H), 4.10 (m, 2H), 3.86 (m, 5H), 3.04 (m, 5H), 0.90 (t, *J* = 7 Hz, 3H).

20 Synthesis of triazole 153

Triazole 153 was made from alkyne 174 and azide 158 using method A as described for compound 149. Data for 153: ¹H-NMR, partial, (500 MHz, CDCl₃) δ 7.50 (s, 1H), 7.29 (dd, *J* = 15, 3 Hz, 1H), 6.94 (dd, *J* = 10, 3 Hz, 1H), 6.87 (t, *J* = 9 Hz, 1H), 5.13 (m, 1H), 5.00 (m, 1H), 4.71 (m, 2H), 4.43 (d, *J* = 7 Hz, 1H), 4.26 (bs, 1H), 3.61 (d, *J* = 8 Hz, 1H), 0.78 (t, *J* = 8 Hz, 3H).

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Synthesis of alkyne 174

Alkyne 174 was made from des(N-methyl)azithromycin 171 and tosylate 161 using the same procedure described for compound 163.

30 Example 7 – Synthesis of Compound 175

Triazole 152 was hydrolyzed with dilute acid to afford the des-cladinose derivative 175.

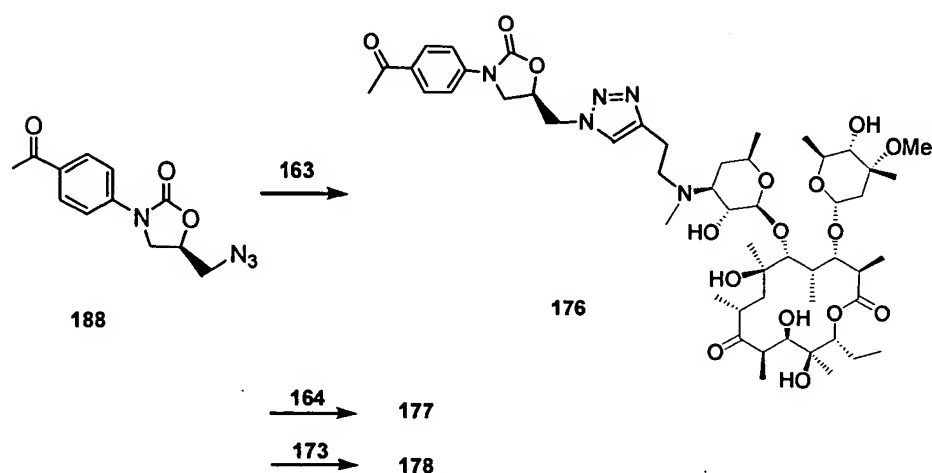
Synthesis of triazole 175

Compound **152** (0.120 g, 0.108 mmol) was dissolved in 0.25N HCl (10 mL) and the solution was kept stirring at room temperature for 24 h. The reaction was extracted with CH₂Cl₂ (2 x 20 mL) and the organic layer was discarded. The aqueous layer was basified with conc. NH₄OH and then extracted with CH₂Cl₂ (3 x 30 mL). The combined organic layer was extracted with saturated brine (1 x 20 mL), and dried over Na₂SO₄. TLC (CH₂Cl₂/MeOH/NH₄OH 10:1:0.05) showed > 95 % conversion to a new lower R_f product (R_f = 0.56). The solvent was evaporated to provide **175** as a white solid (0.101 g, 98%). Data for **175**: ¹H-NMR (300 MHz, CDCl₃, partial): δ 7.58 (s, 1H), 7.26 (dd, *J* = 14, 2 Hz, 1H), 6.91 (dd, *J* = 10, 2 Hz, 1H), 6.82 (t, *J* = 9 Hz, 1H), 4.97 (m, 1H), 4.63-4.66 (m, 3H), 4.36 (d, *J* = 7 Hz, 1H), 4.02 (bs, 1H), 3.78 (t, *J* = 4 Hz, 4H), 2.96 (t, *J* = 5 Hz, 4H), 0.83 (t, *J* = 7 Hz, 3H).

Example 8 – Synthesis of Compounds 176-178

Scheme 34 below depicts the synthesis of compounds **176-178** using the chemistries previously exemplified. Azide **188** was treated with alkyne **163** to afford triazole **176**. The same azide was used to make triazoles **177** and **178** from alkynes **164** and **173** respectively.

Scheme 34



Synthesis of azide 188

The known azide **188** can be synthesized following the procedure reported in the literature (Gregory, W.A. *et al. J. Med. Chem.* **1989**, 32, 1673).

Synthesis of triazole **176**

This compound was made from alkyne **163** and azide **188** using method A as described for compound **149**. Data for **176**: $^1\text{H-NMR}$ (300 MHz, CDCl_3 , partial): δ 7.90 (d, $J = 9$ Hz, 2H), 7.59 (s, 1H), 7.50 (d, $J = 9$ Hz, 2H), 5.01-5.15 (m, 2H), 4.84 (d, $J = 4$ Hz, 1H), 4.71 (m, 2H), 4.36 (d, $J = 7$ Hz, 1H), 4.20 (t, $J = 7$ Hz, 1H) 3.93-4.02 (m, 4H), 3.79 (bs, 1H), 0.79 (t, $J = 7$ Hz, 3H).

Synthesis of triazole **177**

This compound was made from alkyne **164** and azide **188** using method A as described for compound **149**. Data for **177**: $^1\text{H-NMR}$ (300 MHz, CDCl_3 , partial): δ 7.98 (d, $J = 9$ Hz, 2H), 7.53-7.56 (m, 3H), 5.07-5.19 (m, 2H), 4.89 (d, $J = 4$ Hz, 1H), 4.75 (m, 2H), 4.43 (d, $J = 7$ Hz, 1H), 4.22 (t, $J = 7$ Hz, 1H), 4.01 (m, 1H), 3.92 (s, 1H), 3.83 (s, 1H), 0.86 (t, $J = 7$ Hz, 3H).

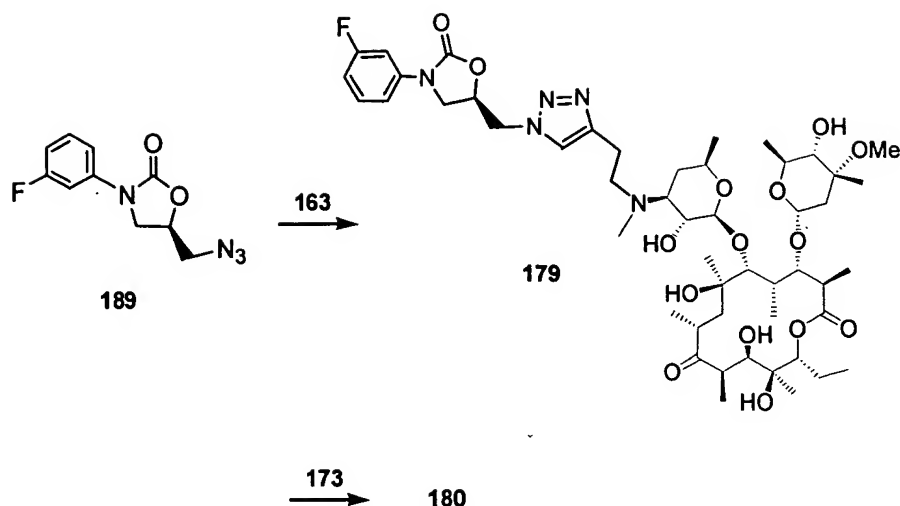
Synthesis of triazole **178**

This compound was made from alkyne **173** and azide **188** using method A as described for compound **149**. Data for **178**: $^1\text{H-NMR}$ (300 MHz, CDCl_3 , partial): δ 7.90 (d, $J = 9$ Hz, 2H), 7.55 (s, 1H), 7.48 (d, $J = 8$ Hz, 2H), 4.97-5.02 (m, 2H), 4.61-4.67 (m, 3H), 4.36 (d, $J = 7$ Hz, 1H), 3.95-4.21 (m, 5H), 3.58 (m, 2H), 3.36 (m, 1H), 3.14-3.25 (m, 5H), 0.82 (t, $J = 7$ Hz, 3H).

Example 9 – Synthesis of Compounds **179-180**

Scheme 35 below depicts the synthesis of compounds **179** and **180** using the chemistries previously exemplified. Azide **189** was treated with alkyne **163** to afford triazole **179**. The same azide was used to make triazole **180** from alkyne **173**.

Scheme 35



Synthesis of azide 189

The azide was synthesized from 3-fluoroaniline using the chemistry reported in the
 5 literature (Brickner, S.J. *et al. J. Med. Chem.* **1996**, *39*, 673).

Synthesis of triazole 179

This compound was made from alkyne **163** and azide **189** using method A as described
 for compound **149**. Data for **179**: $^1\text{H-NMR}$ (300 MHz, CDCl_3 , partial): δ 7.55 (s, 1H), 7.28-7.36
 10 (m, 1H), 7.09 (dd, $J = 8$ Hz, 1.6 Hz, 1H), 6.83 (m, 1H), 5.04-5.12 (m, 2H), 4.88 (d, $J = 5$ Hz,
 1H), 4.72 (m, 2H), 4.39 (d, $J = 7$ Hz, 1H), 4.16 (t, $J = 7$ Hz, 1H), 3.82 (s, 1H), 0.83 (t, $J = 7$ Hz,
 3H).

Synthesis of triazole 180

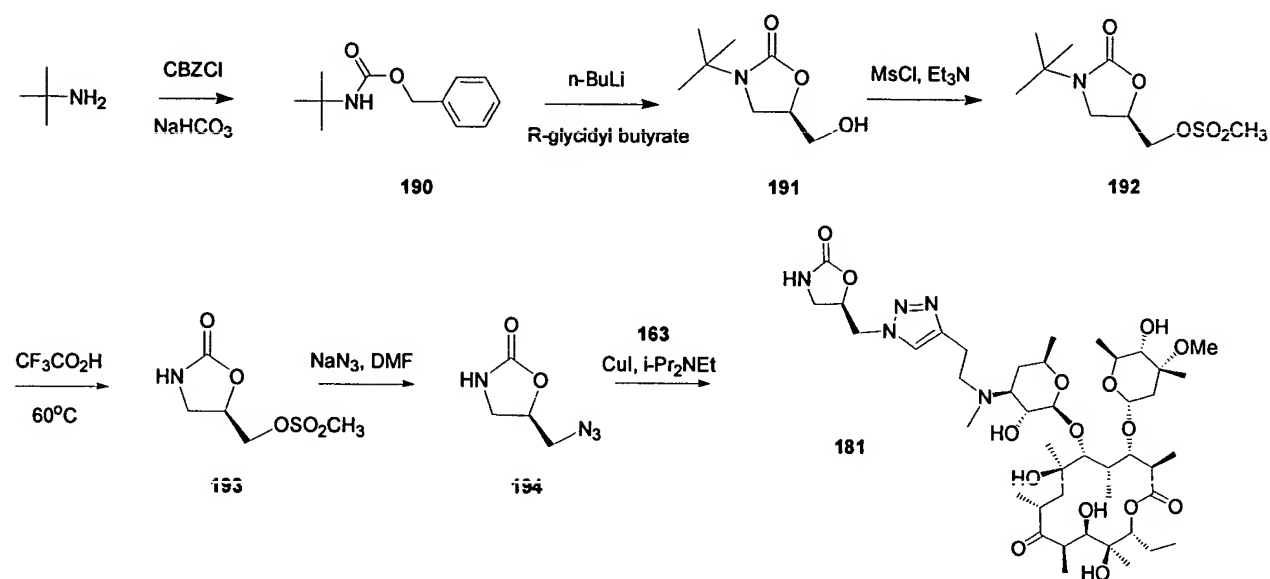
This compound was made from alkyne **173** and azide **189** using method A as described
 for compound **149**. Data for **180**: $^1\text{H-NMR}$ (300 MHz, CDCl_3 , partial): δ 7.55 (s, 1H), 7.22-7.29
 (m, 1H), 7.02 (d, $J = 8$ Hz, 1H), 6.77 (m, 1H), 5.01 (m, 2H), 4.63-4.66 (m, 3H), 4.21-4.37 (m,
 3H), 3.86 (m, 1H), 3.60 (m, 2H), 3.41 (m, 1H), 0.82 (t, $J = 8$ Hz, 3H).

20 Example 10 – Synthesis of Compound 181

Scheme 36 below depicts the synthesis of compound **181** from azide **194** and alkyne **163**.
 The synthesis of azide **194** began with the conversion of tert-butylamine to benzylcarbamate **190**.
 Carbamate **190** was treated with n-butyllithium and R-glycidyl butyrate to afford alcohol **191**.

Mesylation to give **192** was followed by cleavage of the t-butyl group with trifluoroacetic acid to provide mesylate **193**. Displacement of the mesylate with sodium azide yielded azide **194**. The azide was treated with alkyne **163** to afford triazole **181**.

5 Scheme 36



Synthesis of carbamate **190**

- 10 Sodium bicarbonate (34.48 g., 410.4 mmol) was dissolved in water (680 mL) and tert-butylamine (29 mL, 273.6 mmol) was added. The mixture was cooled to 0°C, and benzyl chloroformate (37 mL) was added. The mixture was stirred 5 min at 0°C, the cold bath removed, and then stirring was continued at room temperature overnight (~16 hours). The mixture was
- 15 washed with water, 1N HCl, and then brine. The organic layer was dried with Na₂SO₄, and evaporated to yield **190** (48.45 g., 85% yield) of suitable purity for use in subsequent reactions. Data for **190**: ¹HNMR (300 MHz, CDCl₃): δ 7.37-7.26 (m, 5H), 5.04 (s, 2H), 4.77 (brs, 1H), 1.31 (s, 9H).

20 Synthesis of alcohol **191**

Carbamate **190** (40 g., 193 mmol) was dissolved in 540 mL tetrahydrofuran, and the solution cooled to -78°C. n-Butyllithium (2.5M in hexane, 85 mL, 212.4 mmol) was added

slowly, and the mixture allowed to stir for 45 min at -78°C. R-Glycidyl butyrate (32.6 mL, 212.4 mmol) was added, and the mixture was stirred for 1 h at -78°C. The bath was removed and the reaction allowed to stir overnight at room temperature. The mixture had become thick with solids, and an additional 150 mL of tetrahydrofuran was added, and stirring was continued for another hour. The reaction was quenched with 25 mL saturated ammonium chloride solution, and partitioned with ethyl acetate and water. The aqueous layer was extracted thrice with ethyl acetate, and the combined organic layer was washed with brine, dried (Na₂SO₄), and evaporated to yield **191** (15.21 g., 46% yield) of suitable purity for use in subsequent reactions. Data for **191**: ¹HNMR (300 MHz, CDCl₃): δ 4.29 (dd, *J* = 9, 2 Hz, 1H), 4.19 (dd (app), *J* = 8, 8 Hz, 1H), 3.94-3.87 (m, 1H), 3.84-3.76 (m, 1H), 3.71-3.61 (m, 1H), 2.50-2.42 (m, 1H), 1.44 (s, 9H).

Synthesis of mesylate **192**

Alcohol **191** (9.00 g., 52.0 mmol) was dissolved in 215 mL methylene chloride, and the mixture cooled to 0°C. Triethylamine (14.5 mL, 104 mmol) was added, followed by methanesulfonyl chloride (4.43 mL, 57.2 mmol). The mixture was allowed to warm to room temperature and stirred overnight. Methylene chloride (120 mL) was added, and the mixture washed twice with 1N HCl, then twice with 10% aqueous sodium carbonate, and then brine. The organic phase was dried (Na₂SO₄), and evaporated to half its volume. Hexane was added, and the solvents evaporated to form a white precipitate. Before the solution was allowed to evaporate to dryness, more hexane was added and evaporation continued. Again, before the solution was allowed to evaporate to dryness, it was filtered and the solid collected. The precipitate was dried to afford mesylate **192** (11.16 g., 85% yield). Data for **192**: ¹HNMR (300 MHz, CDCl₃): δ 4.39-4.34 (m, 1H), 4.25-4.23 (m, 2H), 4.18-4.12 (m, 2H), 3.10 (s, 3H), 1.47 (s, 9H).

Synthesis of mesylate **193**

A solution of mesylate **192** (562 mg, 2.20 mmol) in trifluoroacetic acid (8.0 mL) was heated at 60°C for 4 h. The reaction mixture was cooled to room temperature, and the solvent was evaporated. The remaining residue was thrice dissolved in chloroform (50 mL) and evaporated to afford mesylate **193** (450 mg, 100% yield) as a tan solid. Data for **193**: ¹HNMR

(300 MHz, DMSO): δ 7.86 (brs, 1H), 4.34-4.27 (m, 1H), 4.12-4.08 (m, 2H), 4.05-3.98 (m, 2H), 3.14 (s, 3H).

Synthesis of azide 194

5 A solution of mesylate **193** (400 mg, 2.10 mmol) in dimethylformamide (4.0 mL) was treated with sodium azide (195 mg, 3.00 mmol) and the mixture heated to 80°C for 3 h. The reaction mixture was cooled to room temperature, diluted with ethyl acetate (100 mL), and washed with brine (2 x 50 mL). Drying (Na₂SO₄), and evaporation provided azide **194** (105 mg, 35% yield) as a yellow oil of suitable purity for use in subsequent reactions. Data for **194**:
10 ¹HNMR (300 MHz, CDCl₃): δ 6.29 (s, 1H), 4.45-4.40 (m, 1H), 4.13-4.07 (m, 1H), 3.97-3.78 (m, 1H), 3.48-3.35 (m, 2H).

Synthesis of triazole 181

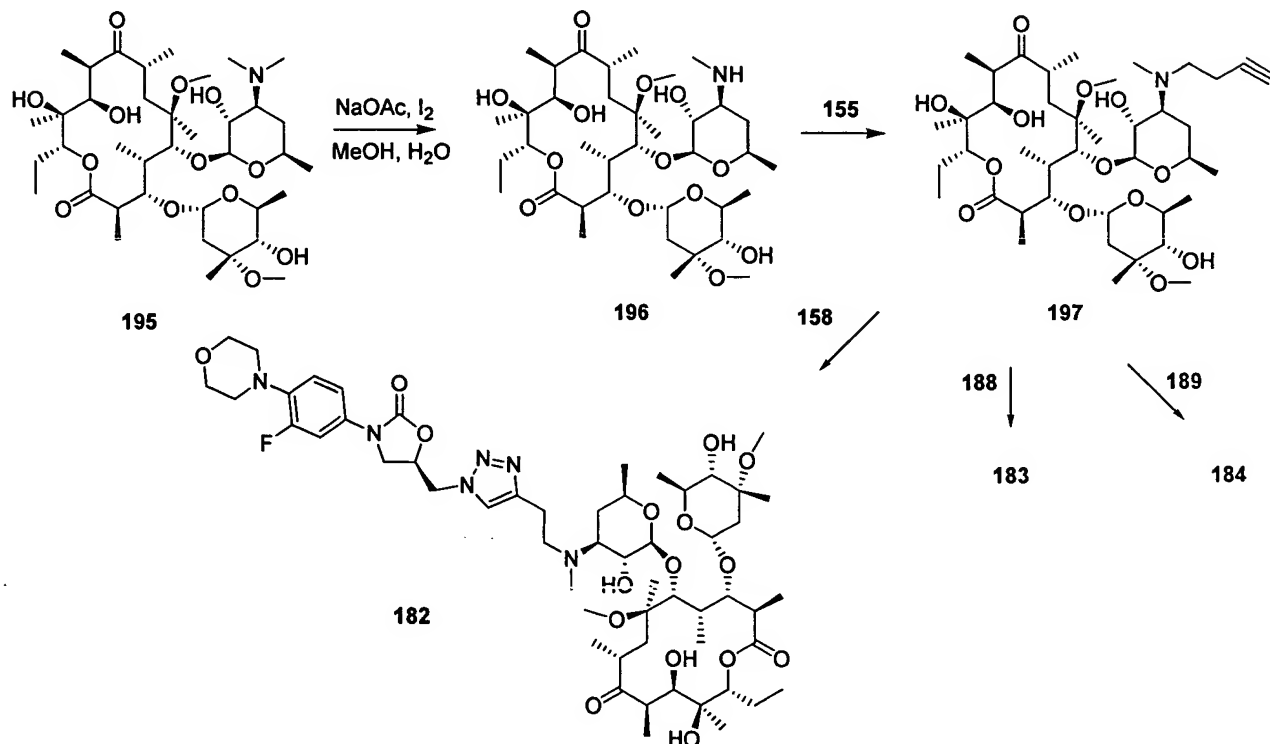
15 A solution of alkyne **163** (135 mg, 0.180 mmol) in tetrahydrofuran (3.0 mL) was treated with azide **194** (50 mg, 0.350 mmol), i-Pr₂N⁺Et⁻ (1.00 mL, 5.30 mmol) and copper (I) iodide (50 mg, 0.270 mmol), and the mixture was stirred under argon at room temperature for 15 h. The reaction mixture was diluted with methylene chloride (100 mL), washed with saturated aqueous NH₄Cl (50 mL), and brine (50 mL). The organic phase was dried (Na₂SO₄), and evaporated. The residue was chromatographed on silica gel using a 5-20% gradient of methanol in 1:1 ethyl
20 acetate/methylene chloride as eluant to provide 80 mg of crude product. The crude was dissolved in methylene chloride (100 mL) and washed with saturated aqueous NH₄Cl (3 x 100 mL) and dried again. Preparative thin layer chromatography (1:4.5:4.5 methanol/methylene chloride/ethyl acetate as eluant) provided triazole **181** (9.0 mg, 6% yield) as a white film. Data for **181**: MS (ESI) *m/z* 914 (M+H)⁺. ¹HNMR (300 MHz, CDCl₃, partial): δ 7.54 (s, 1H), 6.12 (s, 1H), 5.01-
25 4.95 (m, 1H), 4.79 (d, *J* = 4 Hz, 1H), 4.19-4.11 (m, 2H), 4.08-4.02 (m, 2H), 3.83 (s, 1H), 3.74 (s, 1H), 3.48-3.30 (m, 4H), 3.23 (s, 3H), 3.09-2.90 (m, 4H), 2.87-2.73 (m, 4H), 2.70-2.50 (m, 2H), 2.28 (s, 3H), 0.80 (t (app), *J* = 7 Hz, 3H).

Example 11 – Synthesis of Compounds 182-184

30 Scheme 37 below depicts the synthesis of compounds **182-184** starting from clarithromycin (**195**). Clarithromycin is demethylated to afford secondary amine **196** which was

subsequently alkylated with tosylate **155** to provide alkyne **197**. Alkyne **197** was treated with azides **158**, **188**, and **189** to yield triazoles **182**, **183**, and **184** respectively.

Scheme 37



5

Synthesis of amine **196**

To a mixture of clarithromycin (**195**) (1.00 g, 1.3 mmol) and NaOAc·3H₂O (0.885 g, 6.5 mmol) was added MeOH-H₂O (20 mL, 4:1), and the mixture heated to 55-60°C. Iodine (0.330 g, 1.3 mmol) was added portionwise and the reaction stirred at 55-60°C for 3 h. The reaction mixture was poured into 50 mL CHCl₃ containing 1 mL ammonium hydroxide. It was extracted with CHCl₃ (4 x 50 mL), washed with water (70 mL) containing 5 mL ammonium hydroxide, dried (anhydrous Na₂SO₄), concentrated and purified by flash chromatography (silica gel, CHCl₃:MeOH:NH₄OH 100:10:0.1) to afford **196**. Yield: 0.9g (92%).

15

Synthesis of alkyne **197**

To a solution of *N*-desmethyl clarithromycin **196** (3.00 g, 4.08 mmol) and tosylate **155** (1.40 g, 6.13 mmol) in THF (45 mL) was added Hunig's base (15 mL) and the mixture was refluxed for 48 h. The reaction mixture was concentrated under reduced pressure and

redissolved in CHCl_3 (100 mL). The organic layer was washed with brine (3 x 100 mL), dried (over Na_2SO_4), and concentrated under reduced pressure. After purification by flash chromatography (silica gel, 5% MeOH in CHCl_3), 2.50 g (78% yield) of pure product **197** was obtained. Data for **197**: ^1H NMR (300 MHz, CDCl_3 , partial): δ 0.85 (t, 3H), 2.25 (s, 3H), 3.00 (s, 3H), 3.20 (s, 1H), 3.25 (m, 1H), 3.30 (s, 3H), 3.50 (m, 1H), 3.55 (s, 1H), 3.65 (d, 1H), 3.75 (m, 3H), 4.00 (s, 1H), 4.05 (m, 1H), 4.45 (d, 1H), 4.95 (d, 1H), 5.10 (dd, 1H).

Synthesis of triazole **182**

To a solution of alkyne **197** (0.100 g, 0.127 mmol), azide **158** (0.082 g, 0.254 mmol), and Hunig's Base (0.417 mL) in THF (1.5 mL) was added CuI (0.030 g, 0.16 mmol), and the reaction mixture was stirred at room temperature for 2 hours. The reaction mixture was diluted with CHCl_3 (50 mL), washed with saturated NH_4Cl (3 x 50 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude reaction mixture was purified on a silica gel column eluting with 3% 2M NH_3 -MeOH in CH_2Cl_2 to afford 1, 4 triazole isomer **182** (0.125 g).

Data for **182**: ^1H NMR (300 MHz, CDCl_3 , partial): δ 0.85 (t, 3H), 2.25 (s, 3H), 3.65 (d, 1H), 4.10 (t, 1H), 4.40 (d, 1H), 4.70 (dd, 2H), 4.90 (d, 1H), 5.10-4.95 (m, 2H), 6.88 (t, 1H), 7.00 (dt, 1H), 7.35 (dd, 1H), 7.60 (s, 1H).

Synthesis of triazole **183**

The same protocol used above to synthesize target **182** was used for the cycloaddition of alkyne **197** (0.100 g, 0.127 mmol) and azide **188** (0.066 g, 0.254 mmol) to afford target **183**.

Data for **183**: ^1H NMR (300 MHz, CDCl_3 , partial): δ 0.85 (t, 3H), 2.20 (s, 3H), 2.55 (s, 3H), 3.00 (s, 3H), 3.30 (s, 3H), 3.70 (d, 1H), 3.95-4.05 (m, 3H), 4.20 (t, 1H), 4.45 (d, 1H), 4.70 (dd, 2H), 4.90 (d, 1H), 5.10-5.00 (m, 2H), 7.55 (d, 2H), 7.60 (s, 1H), 7.95 (d, 2H).

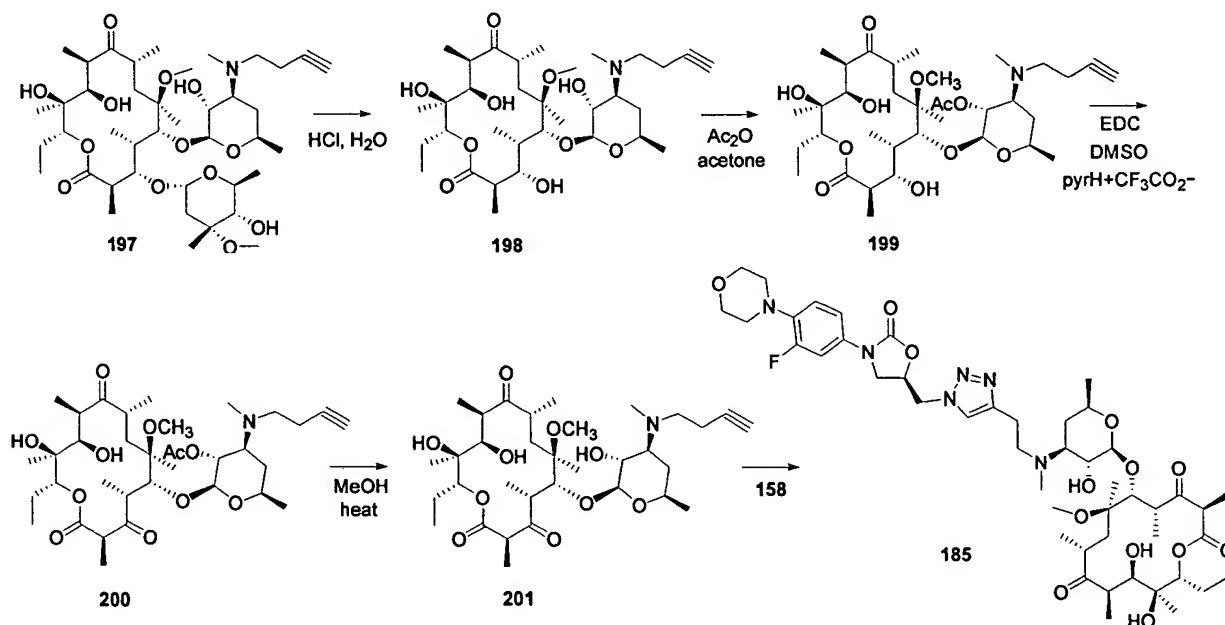
Synthesis of triazole **184**

Cycloaddition of alkyne **197** (0.050 g, 0.0636 mmol) with azide **189** (0.030 g, 0.127 mmol), using the same procedure for the synthesis of **182**, afforded target **184** (0.0253 g). Data for **184**: MS (ESI) m/z 1022.3 ($\text{M}+\text{H}$) $^+$; ^1H NMR (300 MHz, CDCl_3 , partial): δ 0.86 (t, 1H), 2.25 (s, 3H), 3.00 (s, 3H), 3.30 (s, 3H), 3.50 (m, 1H), 3.65 (s, 1H), 4.10 (t, 1H), 4.40 (d, 1H), 4.70 (dd, 2H), 4.85 (d, 1H), 5.00 (m, 2H), 6.85 (bt, 1H), 7.10 (bd, 1H), 7.35 (bt, 2H), 7.60 (s, 1H).

Example 12 – Synthesis of Compound 185

Scheme 38 below depicts the synthesis of compound **185** starting from alkyne **197**. Alkyne **197** is hydrolyzed with dilute acid to afford the des-cladinose derivative **198**. The hydroxyl on the desosamine sugar of **198** was acetylated to afford alcohol **199** which was then oxidized to ketolide derivative **200**. Deacylation of **200** provided alkyne **201**, which was then treated with azide **158** to provide triazole **185**.

Scheme 38



Synthesis of alcohol 198

To the alkyne **197** (0.700 g) was added 10 mL 0.9N HCl and the mixture was stirred for 4 h at room temperature. The reaction mixture was saturated with sodium chloride and was adjusted to pH 8 using aqueous NH_4OH solution. The solution was extracted with ethyl acetate (3 x 30 mL), dried (with Na_2SO_4), and concentrated under reduced pressure. Purification of the crude reaction mixture by flash chromatography (silica gel, 60% ethyl acetate in hexane) afforded 0.200 g (35% yield) of the descladinose derivative **198**. Data for **198**: ^1H NMR (300 MHz, CDCl_3 , partial): δ 0.82 (t, 3H), 2.25 (s, 3H), 3.00 (s, 3H), 3.25 (dd, 1H), 3.55 (m, 2H), 3.70 (s, 1H), 3.85 (s, 1H), 3.95 (s, 1H), 4.40 (d, 1H), 5.15 (dd, 1H).

Synthesis of acetate **199**

To a solution of **198** (0.200 g, 0.32 mmol) in acetone (2 mL) was added acetic anhydride (0.050 mL, 0.5 mmol) and the mixture was stirred overnight at room temperature. The reaction was quenched with water and extracted with ethyl acetate (3 x 50 mL). The combined organic fractions were washed with saturated sodium bicarbonate (3 x 50 mL), dried (anhydrous Na₂SO₄), and concentrated under reduced pressure. The crude reaction mixture was purified by flash chromatography (silica gel, 50% ethyl acetate in hexane) to yield 0.100 g (50% yield) of acetate **199**. Data for **199**: ¹HNMR(300 MHz, CDCl₃, partial): δ 0.84 (t, 3H), 2.00 (s, 3H), 2.20 (s, 3H), 2.90 (s, 3H), 3.00 (q, 1H), 3.25 (s, 1H), 3.47 (m, 2H), 3.70 (bs, 1H), 3.82 (bs, 1H), 3.97 (s, 1H), 4.60 (d, 1H), 4.77 (dd, 1H), 5.15 (dd, 1H).

Synthesis of ketolide **200**

To a solution of acetate **199** (0.090 g, 0.134 mmol), EDC•HCl (0.172 g, 0.90 mmol), and DMSO (0.171 mL, 2.41 mmol) in CH₂Cl₂ (1.5 mL) was added dropwise a solution of pyridinium trifluoroacetate (0.174 g, 0.90 mmol) in CH₂Cl₂ (1 mL) at 15⁰C. The reaction mixture was slowly warmed up to room temperature and stirred for 3 h. The reaction was quenched with water (2 mL), and allowed to stir for 30 min. The mixture was then poured into CHCl₃ (50 mL), and the organic layer was washed with water (2 x 50 mL), dried (over anhydrous Na₂SO₄), and concentrated under reduced pressure. The crude material was purified by flash chromatography (silica gel, 30% ethyl acetate in hexane) to yield 0.070g (78%) of the ketolide **200**. Data for **200**: MS (ESI) *m/z* 668 (M+H)⁺; ¹HNMR (300 MHz, CDCl₃, partial): δ 0.86 (t, 3H), 2.00 (s, 3H), 2.24 (s, 3H), 2.70 (s, 3H), 2.95-3.10 (m, 1H), 3.15-3.05 (m, 1H), 3.45-3.65 (m, 1H), 3.80 (q, 1H), 3.90 (s, 1H), 4.28 (d, 1H), 4.40 (d, 1H), 4.76 (dd, 1H), 5.10 (dd, 1H).

Synthesis of alkyne **201**

A solution of ketolide **200** (0.230 g) in MeOH (10 mL) was heated at 50⁰C for 48 h. The solvent was removed under reduced pressure to yield pure deacetylated product **201** (0.190 g, 88%). Data for **201**: MS (ESI) *m/z* 626 (M+H)⁺; ¹HNMR (300 MHz, CDCl₃, partial): δ 0.85 (t, 3H), 2.25 (s, 3H), 2.70 (s, 3H), 2.97 (q, 1H), 3.10 (t, 1H), 3.18 (dd, 1H), 3.5 (m, 1H), 3.80-3.97 (m, 2H), 4.32 (m, 2H), 5.15 (dd, 1H).

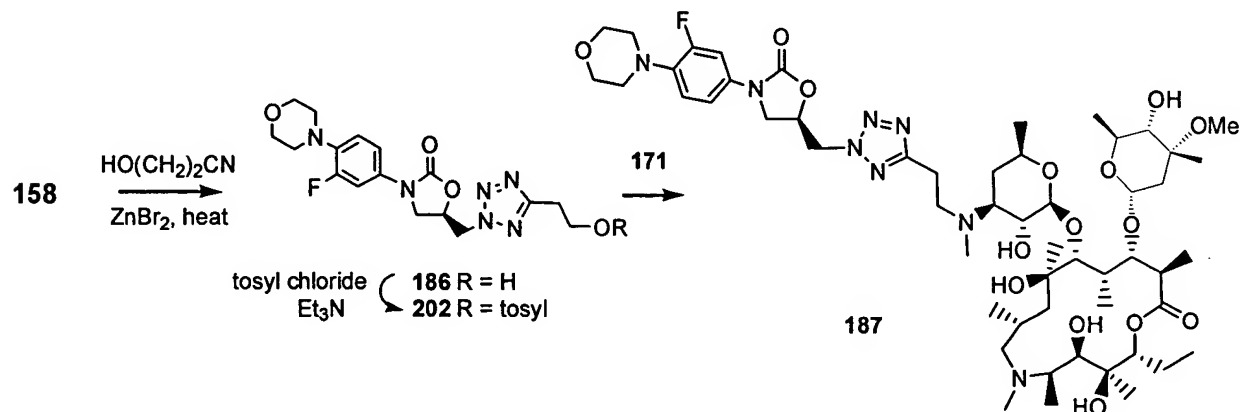
Synthesis of triazole 185

To a solution of **201** (0.050 g, 0.080 mmol), azide **158** (0.050 g, 0.16 mmol), and Hunig's Base (0.417 mL) in THF (1.5 mL) was added CuI (0.030 g, 0.16 mmol), and the reaction mixture was stirred at room temperature for 2 h. It was diluted with CHCl₃ (50 mL), washed with saturated NH₄Cl (3 x 50 mL), dried (anhydrous Na₂SO₄) and concentrated under reduced pressure. The crude reaction mixture was purified by flash chromatography (silica gel, 3% 2M NH₃-MeOH in CH₂Cl₂) to afford **185** (0.043 g). Data for **185**: MS (ESI) *m/z* 947.4 (M+H)⁺; ¹HNMR (300 MHz, CDCl₃, partial): δ 0.86 (t, 3H), 2.25 (s, 3H), 2.70 (s, 3H), 4.10 (t, 1H), 4.30 (t, 2H), 4.70 (dd, 2H), 5.00 (m, 1H), 5.10 (dd, 1H), 6.90 (t, 1H), 6.95 (dt, 1H), 7.25 (dd, 1H) 7.60 (s, 1H).

Example 13 – Synthesis of Compounds 186 and 187

Scheme 39 below depicts the synthesis of compounds **186** and **187**. Azide **158** is treated with 3-hydroxypropionitrile to yield tetrazole **186**. Tetrazole **186** was converted to tosylate **202** which then served to alkylate amine **171** to afford tetrazole **187**.

Scheme 39



Synthesis of tetrazole 186

A suspension of azide **158** (0.300 g, 0.940 mmol), 3-hydroxypropionitrile (1.0 mL, 14.2 mmol) and zinc bromide (ZnBr_2) (0.212 g, 0.940 mmol) in 2-propanol/H₂O (4:1) was heated under reflux for 40 h. The reaction was poured into CH₂Cl₂ (50 mL) and H₂O (20 mL) and

carefully partitioned (caution: emulsion problem). The aqueous layer was back-extracted with CH₂Cl₂ (3 x 30 mL). The combined organic layer was dried over Na₂SO₄ and the solvent was evaporated. The crude was purified on silica gel column eluting with 0-10% MeOH in CH₂Cl₂ to provide **186** (0.037 g, 10%). ¹H-NMR (300 MHz, CDCl₃, partial): δ 7.41 (dd, *J* = 14, 3 Hz, 1H), 7.05-7.13 (m, 2H), 6.93 (t, *J* = 9 Hz, 1H), 4.78 (m, 1H), 3.65- 4.04 (m, 10H), 3.04 (t, *J* = 5 Hz, 4H), 2.48 (t, *J* = 6 Hz, 2H).

Synthesis of tosylate **202**

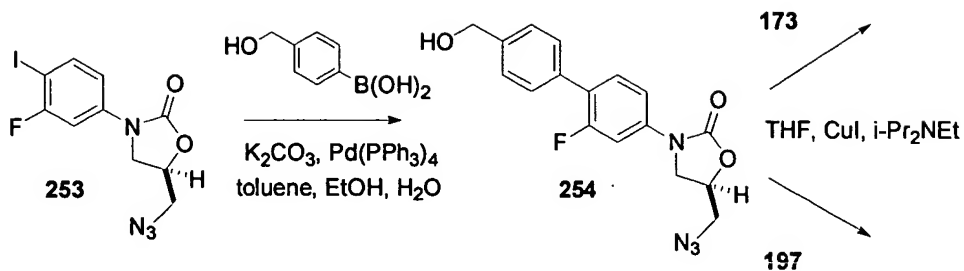
Tetrazole **186** (0.028 g, 0.071 mmol) was dissolved in CH₂Cl₂ (2 mL) and Et₃N (0.015 mL, 0.107 mmol). To this solution was added p-toluenesulfonyl chloride (0.034 g, 0.179 mmol) and stirring was continued at room temperature for 24 h during which time a quantitative consumption of **186** was noticed by TLC (CH₂Cl₂/MeOH 9:1, R_f = 0.52). The reaction was quenched with H₂O/THF 10:1 within 30 min and then partitioned between 10 % NaHCO₃ (15 mL) and CH₂Cl₂ (20 mL). The two layers were separated; the organic layer was washed with saturated brine (3 X 15 mL) and dried over Na₂SO₄. The solvent was evaporated, and the crude was purified on a silica gel column eluting with 0-3 % MeOH in CH₂Cl₂ to provide **202** (0.031g, 80%).

Synthesis of tetrazole **187**

Compound **187** was made from des(N-methyl)-azithromycin **171** and tosyltetrazole **202** using method B as described for compound **149**. Data for **187**: ¹H-NMR (300 MHz, CDCl₃, partial): δ 7.40 (dd, *J* = 14, 3 Hz, 1H), 6.98 (dd, *J* = 9, 2 Hz, 1H), 6.84 (t, *J* = 9 Hz, 1H), 5.05 (m, 1H), 4.62-4.65 (m, 3H), 4.34 (d, *J* = 7 Hz, 1H), 4.19 (bs, 1H), 3.80 (t, *J* = 5 Hz, 4H), 2.98 (t, *J* = 5 Hz, 4H), 0.82 (t, *J* = 7 Hz, 3H).

Example 14 – Synthesis of Compounds **203** and **204**

Scheme 40 below depicts the synthesis of compounds **203** and **204**. Known azide **253** (see: International Patent Application WO 03/035648) was coupled to 4-hydroxymethylphenylboronic acid to yield biaryl azide **254**. Cycloaddition of **254** to alkynes **173** and **197** delivers macrolide targets **203** and **204** respectively.



5 Synthesis of biaryl azide **254**

Azide **253** (0.300 g, 0.830 mmol), and 4-hydroxymethylphenylboronic acid (0.152 g, 1.00 mmol) were dissolved in toluene. Potassium carbonate (0.345 g, 2.50 mmol), tetrakis(triphenylphosphine)palladium (0.040 g, 0.035 mmol), ethanol (3 mL) and water (3 mL) were added, and the reaction was degassed thrice before being heated to reflux for two hours.

- 10 The reaction was allowed to cool to room temperature, and then was partitioned between ethyl acetate (10 mL) and water (10 mL). The layers were separated, and the aqueous phase extracted with ethyl acetate (2 X 10 mL). The combined organic layers were washed with water (10 mL) and brine (10 mL). The organic layer was dried with $MgSO_4$, and evaporated. The crude was purified on silica gel column eluting with 20-50% EtOAc in CH_2Cl_2 to provide **254** (0.163 g, 15 0.476 mmol; 57% yield).

Synthesis of triazole **203**

This compound was obtained from the reaction of alkyne **173** (0.075g, 0.095 mmol) with azide **254** (0.049g, 0.143 mmol) in the presence of CuI (0.029g, 0.143 mmol) in THF (3 mL) and $i-Pr_2NEt$ (0.6 mL) at room temperature within 6 h. The crude reaction was concentrated and then purified on silica gel eluting with CH_2Cl_2 / MeOH/ NH_4OH 30:1:0.05 to 25:1:0.05 to 20:1:0.05 to 18:1:0.05 to 15:1:0.05 to give **203** as a white solid. Data for **203**: MS (ESI) m/z 1129.4 ($M+H$)⁺; 1H -NMR (300 MHz, $CDCl_3$, partial): δ 7.65 (s, 1H), 7.53-7.33 (m, 6H), 7.19 (d, J = 8 Hz, 1H), 5.03 (m, 2H), 4.70-4.76 (m, 5H), 4.42 (d, J = 7 Hz, 1H), 4.28 (d, J = 3 Hz, 1H), 4.06 (m, 3H), 25 3.67 (m, 2H), 3.43 (m, 1H), 0.82 (m, 7H).

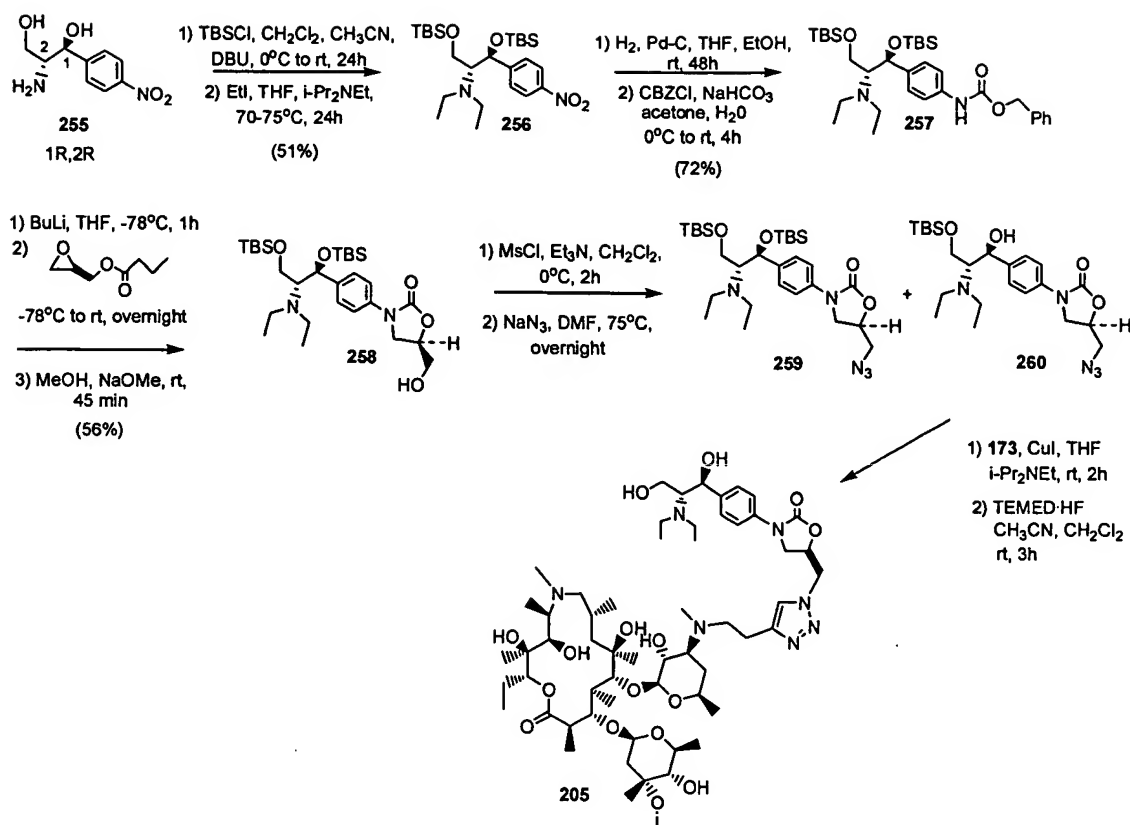
Synthesis of triazole **204**

A solution of alkyne **197** (100 mg, 0.127 mmol) in tetrahydrofuran (3.0 mL) was treated with azide **254** (50 mg, 0.15 mmol), *i*-Pr₂NEt (0.664 mL, 3.81 mmol) and copper (I) iodide (48.4 mg, 0.254 mmol), and the mixture was stirred under argon at room temperature for 15 h. The reaction mixture was diluted with methylene chloride (50 mL), washed with saturated aqueous NH₄Cl (3 x 50 mL), and brine (2 x 50 mL). The organic phase was dried (Na₂SO₄), and evaporated. The residue was chromatographed on silica gel using a 4-10% gradient of methanol in chloroform as eluant to provide 69 mg of pure product **204** as a white powder. Data for **204**: MS (ESI) *m/z* 1128.5 (M+H)⁺, 1150.4 (M+Na)⁺. ¹HNMR (300 MHz, CDCl₃, partial): δ 7.72 (s, 1H), 7.52-7.38 (m, 6H), 7.17 (dd, *J* = 8, 2 Hz, 1H) 5.06-5.03 (m, 2H), 4.92 (d, *J* = 4 Hz, 1H), 4.42 (d, *J* = 7 Hz, 1H), 4.18 (t, 1H), 0.82 (t, *J* = 7 Hz, 3H).

Example 15 – Synthesis of Compound **205**

Scheme 41 depicts the synthesis of compound **205**. Available amine **255** was bis-silylated and the amine alkylated to afford diethyl amine derivative **256**. The nitro group of **256** was reduced and the resultant amine converted to the benzyl carbamate **257**. Conversion of **257** via standard methods to the oxazolidinone **258** was followed by formation of the azides **259** and **260**. Azide **260** was treated with alkyne **173** to afford the triazole cycloadduct which was subsequently desilylated to afford compound **205**.

Scheme 41



Synthesis of amine **256**

To a suspension of amine **255** (2.00 g, 9.33 mmol) in a 1.0 M CH₂Cl₂ solution of TBSCl (22.40 mL, 22.40 mmol) and anhydrous CH₃CN (10 mL) was added DBU (2.96 mL, 19.56 mmol) at 0°C. A clear homogenous solution resulted within a few minutes of the DBU addition and the reaction was stirred at room temperature for 24 h. The reaction was poured into CH₂Cl₂ (60 mL) and extracted with saturated NaHCO₃ (3 x 30 mL), saturated NH₄Cl (2 x 30 mL), saturated brine, and then the organic phase was dried over Na₂SO₄. The solvent was evaporated to give a light yellow oil which was used without further purification.

To a solution of the crude product obtained above (2.00 g, 4.54 mmol) in THF (25 mL) and i-Pr₂NEt (10 mL) was added iodoethane (5.00 mL, 61.35 mmol) and the mixture was heated between 70°C to 75°C for 48 h. The reaction was worked-up as described in the first step above. The crude was purified on silica gel eluting with hexanes/EtOAc 12:1 to 8:1 to give compound **256** as a light yellow oil (1.16 g, 51%). Data for **256**: ¹H-NMR, (300 MHz, CDCl₃): δ 8.08 (d, *J* = 9 Hz, 2H), 7.41 (d, *J* = 9 Hz, 2H), 4.99 (d, *J* = 3 Hz, 1H), 3.79 (m, 1H), 3.65 (m, 1H), 2.59 (m,

2H), 2.48 (m, 1H), 2.37 (m, 2H), 0.86 (s, 9H), 0.84 (s, 9H), 0.63 (t, $J = 7$ Hz, 6H), 0.00 (bs, 9H), -0.29 (s, 3H).

Synthesis of carbamate **257**

5 Compound **256** (1.16 g, 2.34 mmol) was dissolved in absolute EtOH (30 mL) and THF (6 mL). To this solution was added Pd-C (10 wt %, Degussa, 0.11 g) and the reaction was kept under a hydrogen environment using a balloon. TLC after stirring for 48 h revealed a complete consumption of starting material. The reaction was filtered and the filtrate evaporated to give a yellow oil. The crude oil was dissolved in acetone (30 mL) and water (10 mL). The resulting
10 mixture was kept at 0°C while NaHCO₃ (0.46 g, 5.5 mmol) and CBZCl (0.42 mL, 2.81 mmol) were added. The reaction was allowed to warm up to room temperature and stirred for 4 h. The reaction was poured into CH₂Cl₂ (60 mL) and extracted with saturated NaHCO₃ (3 x 30 mL), saturated NH₄Cl (2 x 30 mL), and the organic phase was dried over Na₂SO₄. The solvent was evaporated to give a yellow oil. The crude was purified on silica gel column, eluting with 1-4 %
15 MeOH in CH₂Cl₂ to give **257** as a yellow oil (1.02 g, 72%). Data for **257**: ¹H-NMR (300 MHz, CDCl₃): δ 7.37-28 (m, 9H), 5.17 (s, 2H), 4.84 (d, $J = 4$ Hz, 1H), 3.77 (m, 1H), 3.60 (m, 1H), 2.69-2.43 (m, 5H), 0.88 (s, 9H), 0.85 (s, 9H), 0.75 (t, $J = 7$ Hz, 6H), 0.00 (bs, 9H), -0.29 (s, 3H).

Synthesis of alcohol **258**

20 Carbamate **257** (1.02 g, 1.69 mmol) was dissolved in anhydrous THF (10 mL) and the solution was cooled to -78°C. n-Butyllithium (2.5 M in Hexanes) (0.87 mL, 2.18 mmol) was added and the reaction was maintained at -78°C for 1h. (R)-Glycidyl butyrate (0.31 mL, 2.184 mmol) was added, the reaction was allowed to warm up to room temperature and stirred for about 16 h. The reaction was partitioned between saturated NH₄Cl (30 mL) and CH₂Cl₂ (50
25 mL). The organic layer was washed with saturated NH₄Cl (2 x 30 mL), saturated brine (1 x 30 mL), and then dried over Na₂SO₄. The solvent was evaporated, and the residue was dissolved in MeOH (20 mL) containing a catalytic amount of sodium methoxide, and the solution was stirred at room temperature for 45 min. The solvent was evaporated, the crude was taken up into CH₂Cl₂ (50 mL) and extracted with saturated NH₄Cl (2 x 30 mL). The organic phase was dried over
30 Na₂SO₄ and concentrated. The residue was purified on silica gel column, eluting with 5-6 % MeOH in CH₂Cl₂ to give **258** as a white foam (0.53 g, 56%). Data for **258**: ¹H-NMR (300 MHz,

CDCl₃): δ 7.52 (d, J = 9 Hz, 2H), 7.41 (d, J = 9 Hz, 2H), 4.87 (d, J = 3 Hz, 1H), 4.70 (m, 1H), 4.02-3.92 (m, 3H), 3.76 (m, 2H), 3.62 (m, 1H), 2.63-2.43 (m, 5H), 0.88 (s, 9H), 0.85 (s, 9H), 0.74 (t, J = 7 Hz, 6H), 0.00 (bs, 9H), -0.28 (s, 3H).

5 Synthesis of azides **259** and **260**

To a solution of oxazolidinone **258** (0.53 g, 0.935 mmol) in anhydrous CH₂Cl₂ (15 mL) and Et₃N (0.28 mL, 2.00 mmol) at 0°C was added MsCl (0.14 mL, 1.8 mmol). The reaction was stirred at 0°C for 2 h and the reaction was poured into saturated NaHCO₃ (30 mL) and CH₂Cl₂ (50 mL) and the two layers were separated. The organic layer was extracted with H₂O (2 x 30 mL), saturated brine (1 x 30 mL), and dried over Na₂SO₄. The solvent was evaporated to give a yellow oil. The crude was taken up in DMF (10 mL), NaN₃ (0.24 g, 3.74 mmol) was added, and the reaction was heated at 75°C for 24 h. Water (40 mL) was added and the reaction was extracted with EtOAc (3 x 40 mL). The combined organic layer was extracted with saturated brine (1 x 50 mL) and dried over Na₂SO₄. The solvent was evaporated and the crude was purified on a silica gel column, eluting with 1-6 % MeOH in CH₂Cl₂ to give azide **259** (0.378 g) and azide **260** (0.027 g). Data for azide **259**: ¹H-NMR (300 MHz, CDCl₃): δ 7.54 (d, J = 9 Hz, 2H), 7.41 (d, J = 9 Hz, 2H), 4.87 (d, J = 3 Hz, 1H), 4.70 (m, 1H), 4.02-3.92 (m, 3H), 3.77-3.74 (m, 2H), 3.62 (m, 1H), 2.63-2.43 (m, 5H), 0.88 (s, 9H), 0.85 (s, 9H), 0.71 (t, J = 7 Hz, 6H), 0.00 (bs, 9H), -0.28 (s, 3H). Data for azide **260**: MS (ESI) m/z 478.1 (M+H)⁺; ¹H-NMR (300 MHz, CDCl₃): δ 7.59 (d, J = 9 Hz, 2H), 7.49 (d, J = 9 Hz, 2H), 4.86 (m, 1H), 4.46 (d, J = 10 Hz, 1H), 4.20 (t, J = 9 Hz, 1H), 3.95 (m, 1H), 3.81-3.61 (m, 4H), 2.98-2.94 (m, 2H), 2.79-2.71 (m, 3H), 1.22 (t, J = 7 Hz, 6H), 0.93 (s, 9H), 0.00 (s, 3H), 0.00 (s, 3H).

Synthesis of compound **205**

Alkyne **173** (0.038 g, 0.045 mmol) and azide **260** (0.027g, 0.057 mmol)-were subjected to the cycloaddition reaction in the presence of CuI (0.029g, 0.143 mmol) in THF (3 mL) and *i*-Pr₂NEt (0.6 mL) at room temperature for 2h. The reaction was poured into a mixture containing saturated NH₄Cl/NH₄OH (pH = 9.5, 30 mL) and extracted with CH₂Cl₂ (3 x 30 mL). The combined organic layer was dried over Na₂SO₄ and the solvent evaporated. The crude was purified on silica gel eluting with CH₂Cl₂/MeOH/NH₄OH 15:1:0.05 to give a white solid (0.048 g).

The product obtained above (0.047 g) was dissolved in CH₂Cl₂ (2 mL) and a freshly prepared solution of 1.34 M *N, N,N,N'*-tetramethylethylenediamine hydrofluoride (TEMED·HF) in acetonitrile (0.5 mL, 0.67 mmol) was added. Stirring was continued for 3 h and the reaction was concentrated. The crude was purified on a silica gel column, eluting with CHCl₃/

5 MeOH/NH₄OH 15:1:0.05 to give a slightly impure white solid. This was re-purified on a second silica gel column eluting with CH₂Cl₂/MeOH/NH₄OH 18:1:0.04 to 16:1:0.04 to give **205** as a white solid (0.018 g). Data for **205**: MS (ESI) *m/z* 1172.5 (M+Na)⁺; ¹H-NMR (300 MHz, CDCl₃, partial): δ 7.61 (s, 1H), 7.25-7.17 (m, 4H), 4.89 (m, 2H), 4.58 (m, 3H), 4.17 (d, *J* = 9 Hz, 1H), 4.04 (m, 2H), 3.76 (m, 1H), 3.46-3.31 (m, 4H), 2.85 (d, *J* = 9 Hz, 1H), 0.75 (m, 7H).

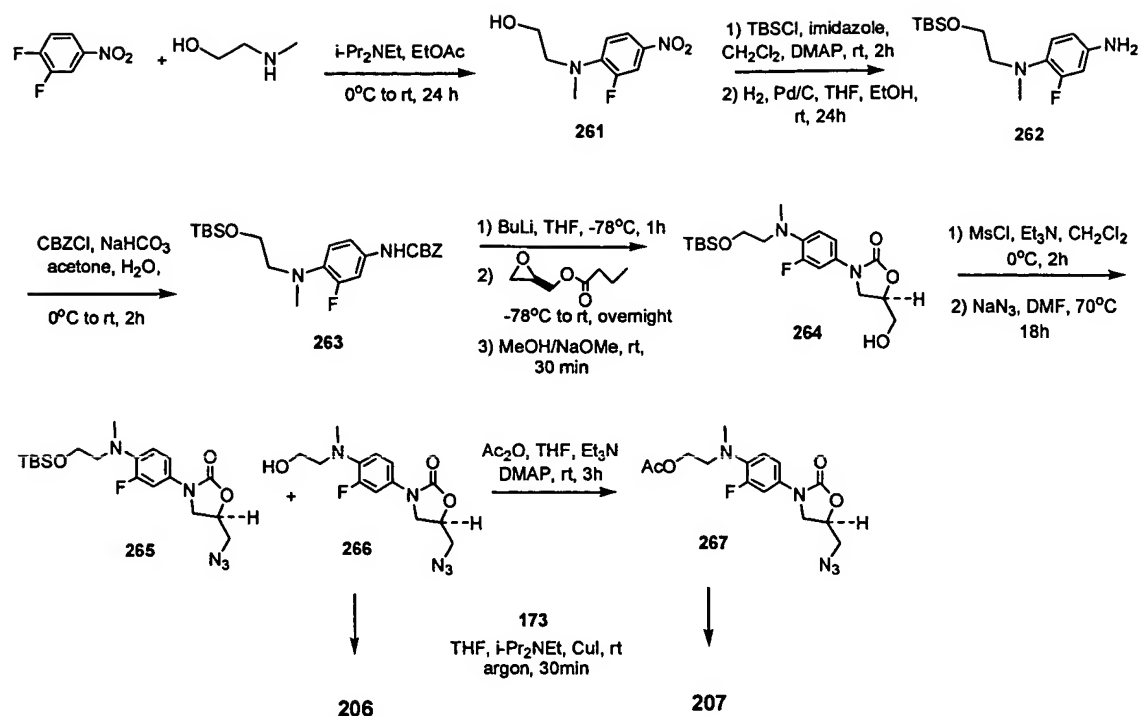
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Example 16 – Synthesis of Compounds 206 and 207

Scheme 42 depicts the synthesis of targets **206** and **207**. The aromatic substitution reaction of 3,4-difluoronitrobenzene and 2-(methylamino)ethanol provided nitroaniline **261**. The alcohol of **261** was protected and the nitro group was reduced to afford amine **262**. Conversion
15 of **262** to carbamate **263** was followed by synthesis of the oxazolidinone **264**. Alcohol **264** was converted to azides **265** and **266**, and the latter was acylated to afford azide **267**. The cycloaddition of **266** and **267** with alkyne **173** afforded targets **206** and **207** respectively.

Scheme 42

20



Synthesis of amine **261**

To a solution of 3,4-difluoronitrobenzene (2.4 mL, 29.72 mmol) in EtOAc (20 mL) and $i\text{-Pr}_2\text{NEt}$ (5.1 mL, 29.30 mmol) was slowly added 2-(methylamino)ethanol (3 mL, 27.10 mmol) at 0°C . The reaction was allowed to warm up to room temperature and stirring was continued overnight. The reaction was poured into EtOAc (30 mL) and extracted with H_2O (50 mL). The aqueous layer was basified with KOH pellets (pH 10.0) and extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layer was dried over Na_2SO_4 and the solvent evaporated to give a yellow solid residue. The crude was dissolved in 6 N HCl (60 mL) at 0°C , extracted with CH_2Cl_2 (3 x 30 mL), and the organic layer was back extracted with 6 N HCl (25 mL). The combined acid layer was basified with KOH pellets at 0°C and extracted with CH_2Cl_2 (4 x 40 mL). The organic phase was dried over Na_2SO_4 and the solvent evaporated to give **261** as a yellow solid ($R_f = 0.56$, $\text{CH}_2\text{Cl}_2/\text{MeOH}$, 4.59 g, 79%). Data for **261**: MS (ESI) m/z 214.7 ($\text{M}+\text{H}$) $^+$.

Synthesis of amine **262**

Compound **261** (4.5 g, 21 mmol), imidazole (2.91 g, 42 mmol) and DMAP (0.26 g, 2.1 mmol) were dissolved in anhydrous CH_2Cl_2 (50 mL). To this solution was added TBSCl (3.33 g, 22.10 mmol) and stirring was continued for 2 h. CH_2Cl_2 (30 mL) was added and the mixture was

extracted with saturated NaHCO₃ (2 x 50 mL) and saturated brine (1x 50 mL). The organic phase was dried over Na₂SO₄ and evaporated to give a yellow oil. The oil was dissolved in absolute EtOH (50 mL) and THF (10 mL). To this solution was added Pd-C (10 wt %, Degussa, 0.50 g) and the reaction was kept under a hydrogen environment using a balloon. TLC after stirring for 24 h revealed a complete consumption of starting material. The reaction was filtered and the filtrate evaporated to give **262** as a red oil which was used in further reactions without further purification. Data for **262**: MS (ESI) *m/z* 298.7 (M+H)⁺.

Synthesis of oxazolidinone **264**

Crude oil **262** was dissolved in acetone (60 mL) and water (20 mL). The resulting mixture was kept at 0°C, and NaHCO₃ (4.13 g, 49.40 mmol) and CBZCl (3.77 mL, 25.22 mmol) were added. The reaction was allowed to warm up to room temperature and stirring continued for 2 h. The reaction was poured into CH₂Cl₂ (120 mL) and extracted with saturated NaHCO₃ (2 x 50 mL) and saturated brine (1 x 50 mL). The organic phase was dried over Na₂SO₄ and evaporated to give carbamate **263** as a red oily residue.

The crude **263** above was dissolved in anhydrous THF (50 mL) and the solution was cooled to -78°C. n-Butyllithium (2.5 M in Hexanes) (10.8 mL, 27 mmol) was added and the reaction was maintained at -78°C for 1h. (R)-Glycidyl butyrate (3.83 mL, 27 mmol) was added, the reaction was allowed to warm up to room temperature, and stirring was continued for about 16 h. The reaction was poured into EtOAc (100 mL), extracted with saturated NaHCO₃ (2 x 60 mL) and saturated brine (1 x 60 mL). The organic phase was dried over Na₂SO₄ and evaporated. The residue was dissolved in MeOH (50 mL) containing sodium methoxide (25 % wt/vol in MeOH, 0.3 mL) and the solution was stirred at room temperature for 30 min. The solvent was evaporated, and the crude was poured into EtOAc (100 mL), and washed with saturated NaHCO₃ (1 x 60 mL) and saturated brine (1 x 60 mL). The organic phase was dried over Na₂SO₄ and evaporated to give a brown oily residue. The residue was purified on a silica gel column, eluting with CH₂Cl₂/MeOH 25:1 to 20:1 to give **264** as a brown solid (5.93 g, 71%). Data for **264**: MS (ESI) *m/z* 399.0 (M+H)⁺.

Synthesis of azides **265** and **266**

To a solution of oxazolidinone **264** (3.00 g, 7.54 mmol) in anhydrous CH₂Cl₂ (40 mL) and Et₃N (2.16 mL, 15.45 mmol) at 0°C was added MsCl (1.03 mL, 13.20 mmol). The reaction was stirred at 0°C for 2 h and then was poured into saturated NaHCO₃ (60 mL) and CH₂Cl₂ (100 mL) and the two layers separated. The organic layer was extracted with H₂O (2 x 40 mL),

5 saturated brine (1 x 40 mL) and dried over Na₂SO₄. The solvent was evaporated to give a brown oil. The crude was taken up in DMF (25 mL), then NaN₃ (2.00 g, 30.16 mmol) was added and the reaction was kept at 70°C for 18 h. Water (60 mL) and EtOAc (100 mL) were added and the two layers separated. The aqueous layer was extracted with EtOAc (2 x 50 mL), and the combined organic layer was dried over Na₂SO₄ and evaporated. The crude was purified on a
10 silica gel column, eluting with CH₂Cl₂/MeOH 30:1 to 24:1 to 20:1 to give azide **265** (2.16 g, 68 %, white solid) and azide **266** (0.33 g, 14 %, brown foam). Data for azide **265**: MS (ESI) *m/z* 424.0 (M+H)⁺; ¹H-NMR (300 MHz, CDCl₃): δ 7.35 (dd, *J* = 15, 3 Hz, 1H), 7.06 (dd, *J* = 9, 2 Hz, 1H), 6.88 (m, 1H), 4.75 (m, 1H), 4.02 (t, *J* = 9 Hz, 1H), 3.81-3.74 (m, 3H), 3.67 (dd, *J* = 13, 5 Hz, 1H), 3.57 (dd, *J* = 13, 4 Hz, 1H), 3.28 (t, *J* = 6 Hz, 2H), 2.90 (s, 3H), 0.85 (s, 9H), 0.01 (s,
15 6H). Data for azide **266**: MS (ESI) *m/z* 309.8 (M+H)⁺; ¹H-NMR (300 MHz, CDCl₃): δ 7.37 (dd, *J* = 15, 3 Hz, 1H), 7.06 (dd, *J* = 9, 3 Hz, 1H), 6.94 (t, *J* = 6 Hz, 1H), 4.77 (m, 1H), 4.03 (t, *J* = 9 Hz, 1H), 3.80-3.56 (m, 5H), 3.20 (t, *J* = 6 Hz, 2H), 2.81 (s, 3H).

Synthesis of azide **267**

20 To a solution of azide **266** (0.16 g, 0.52 mmol) in THF (5 mL) and Et₃N (0.10 mL, 0.68 mmol) was added Ac₂O (0.065 mL, 0.68 mmol) and a few grains of DMAP at room temperature. Stirring was continued for 3 h, then the reaction was quenched with aqueous MeOH, poured into NaHCO₃ (30 mL), and extracted with CH₂Cl₂ (50 mL). The CH₂Cl₂ layer was extracted once with saturated brine (30 mL) and dried over Na₂SO₄. The solvent was evaporated to give **267** as
25 a brown oil (0.182 g, 99%). MS (ESI) *m/z* 351.9 (M+H)⁺.

Synthesis of triazole **206**

This compound was obtained from the reaction of alkyne **173** (0.315 g, 0.40 mmol) with azide **266** (0.16 g, 0.52 mmol) in the presence of CuI (0.057 g, 0.30 mmol) in THF (10 mL) and
30 *i*-Pr₂NEt (0.1 mL) at room temperature within 30 min under argon. Saturated NH₄Cl (30 mL) was added, and stirring was continued for 5 min. The reaction was basified with NH₄OH to pH

9.0. CH₂Cl₂ (40 mL) was added, the two layers were separated, and the aqueous layer was extracted with CH₂Cl₂ (2 x 25 mL). The combined organic layer was dried over Na₂SO₄ and the solvent evaporated. The crude was purified on silica gel eluting with CH₂Cl₂/MeOH/NH₄OH 18:1:0.05 to 15:1:0.05 to 12:1:0.05 to give **206** as a white solid (0.426 g, 97%). Data for **206**:

5 MS (ESI) *m/z* 1096.4 (M+H)⁺; ¹H-NMR (300 MHz, CDCl₃, partial): δ 7.61 (s, 1H), 7.24 (dd, *J* = 15, 2 Hz, 1H), 6.90 (m, 2H), 5.00 (m, 2H), 4.69 (m, 3H), 4.43 (d, *J* = 7 Hz, 1H), 4.24 (m, 2H), 3.88 (m, 1H), 3.74 (t, *J* = 5 Hz, 2H), 0.88 (m, 7H).

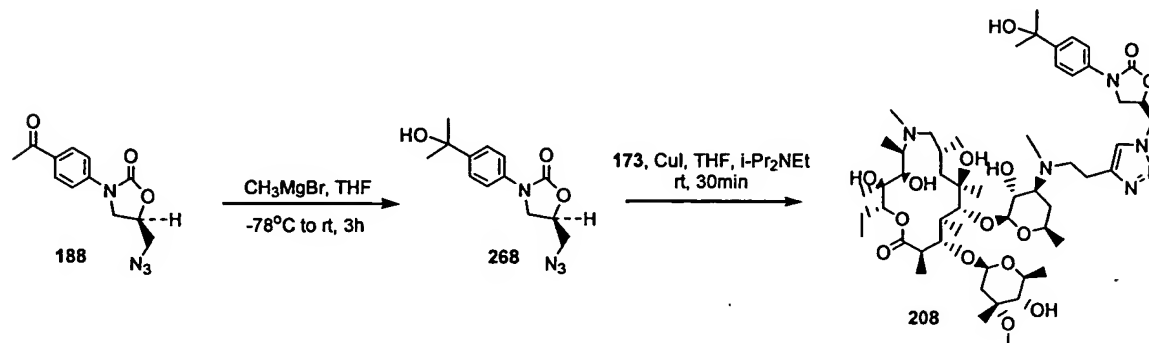
Synthesis of triazole **207**

10 This compound was obtained from the reaction of alkyne **173** (0.315 g, 0.40 mmol) with azide **267** (0.182 g, 0.52 mmol) as described for triazole **206** above. The crude was purified on silica gel, first eluting with CH₂Cl₂/MeOH 18:1 to remove unreacted **267**, then with CH₂Cl₂/MeOH 15:1 to 12:1 to 10:1 containing a trace amount of NH₄OH to give **207** as a white solid (0.42 g, 92%). Data for **207**: MS (ESI) *m/z* 1138.3 (M+H)⁺; ¹H-NMR (300 MHz, CDCl₃, partial): δ 7.62 (s, 1H), 7.29 (dd, *J* = 15, 2 Hz, 1H), 6.93 (m, 1H), 6.85 (t, *J* = 9 Hz, 1H), 5.01 (m, 2H), 4.66 (m, 3H), 4.22 (t, *J* = 6 Hz, 2H), 3.89 (m, 1H), 3.38 (t, *J* = 6 Hz, 2H), 0.89 (m, 7H).

Example 17 – Synthesis of Triazole **208**

20 Scheme 43 depicts the synthesis of triazole **208**. Azide **188** was converted to benzylic alcohol **268**, which was subsequently converted to triazole **208** using the copper-catalyzed cycloaddition chemistry described above.

Scheme 43



Synthesis of azide **268**

A solution of azide **188** (0.38 g, 1.43 mmol) in anhydrous THF (5 mL) was cooled to -78°C. To this solution was slowly added 1 M methyl magnesiumbromide (CH₃MgBr) in butyl ether (1.5 mL, 1.50 mmol) within 20 min. The reaction was allowed to warm up to room temperature and stirring was continued for 3 h. The reaction was quenched with H₂O (20 mL) and extracted with CH₂Cl₂ (40 mL). The organic layer was extracted with saturated brine (25 mL), dried over Na₂SO₄ and the solvent evaporated. The crude was purified on silica gel eluting with EtOAc/Hexanes 3:1 to 5:1 to give azide **268** as a white foam (0.178 g, 45%). Data for **268**: MS (ESI) *m/z* 276.8 (M+H)⁺.

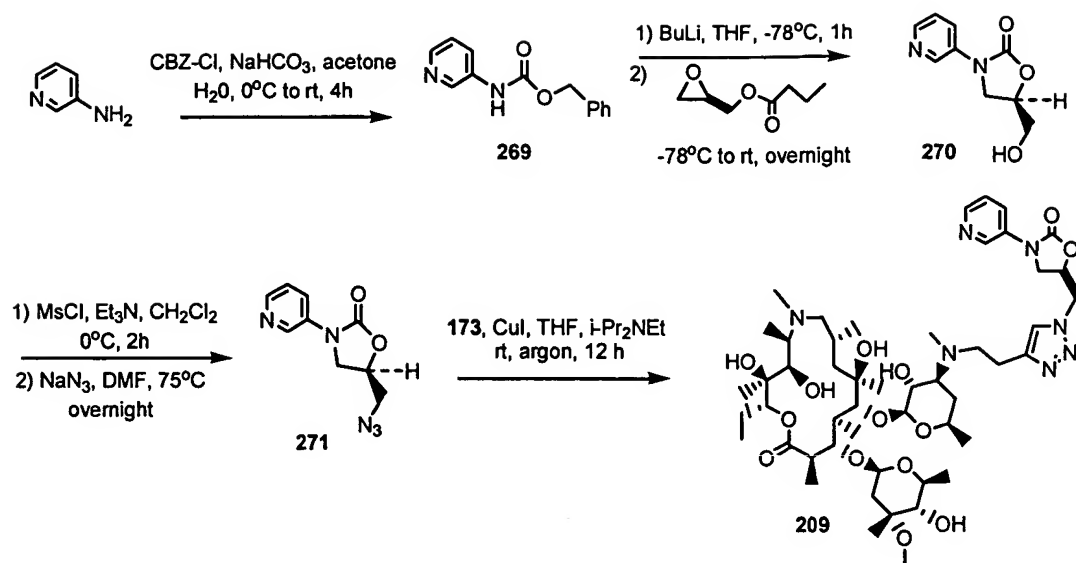
10 Synthesis of triazole **208**

This compound was obtained from the reaction of alkyne **173** (0.20 g, 0.25 mmol) with azide **268** (0.095 g, 0.34 mmol) as described for triazole **206** above except that the reaction was first quenched with saturated NH₄Cl/NH₄OH 5:1 (pH = 9.5, 30 mL) before the usual CH₂Cl₂ extraction. The crude was purified on silica gel, first eluting with CH₂Cl₂/MeOH 12:1, then with CH₂Cl₂/MeOH/NH₄OH 15:1:0.05 to 12:1:0.05 to give **208** as a white solid (0.056 g). Data for **208**: MS (ESI) *m/z* 1063.4 (M+H)⁺; ¹H-NMR (300 MHz, CDCl₃, partial): δ 7.63 (s, 1H), 7.48 (d, *J* = 9 Hz, 2H), 7.37 (d, *J* = 9 Hz, 2H), 5.03 (m, 2H), 4.72 (m, 3H), 4.44 (d, *J* = 7 Hz, 1H), 4.30 (d, *J* = 5 Hz, 1H), 4.16 (t, *J* = 9 Hz, 1H), 3.92 (m, 1H), 3.67 (m, 2H), 0.90 (m, 7H).

20 Example 18 – Synthesis of Triazole **209**

Scheme 44 shows the synthesis of triazole **209**. 3-Aminopyridine was converted to carbamate **269** which was subsequently transformed to azide **271** using chemistry similar to that reported above. Cycloaddition of **271** with alkyne **173** yielded triazole **209**.

25 Scheme 44



Synthesis of alcohol 270

Oxazolidinone **270** was synthesized from 3-aminopyridine using the chemistry reported for the conversion of amine **262** to alcohol **264** (Example 16). The crude was purified on silica gel column, eluting with CH₂Cl₂/MeOH 19: 1 to give **270** as a white solid (46%). Data for **270**: MS (ESI) *m/z* 194.7 (M+H)⁺.

Synthesis of azide 271

Azide **271** was synthesized from alcohol **270** as described for the synthesis of azides **259** and **260** (Example 15) except that the sodium azide reaction with the intermediate mesylated derivative of **270** was complete within 2 h. The reaction was worked-up with saturated NaHCO₃ (30 mL) and EtOAc (4 x 40 mL). The organic phase was dried over Na₂SO₄ and evaporated. The crude was purified on silica gel, eluting with CH₂Cl₂/MeOH 17: 1 to give **271** as a colorless, thick oil (81%). Data for **271**: MS (ESI) *m/z* 220.0 (M+H)⁺; ¹H-NMR (300 MHz, CDCl₃): δ 8.60 (d, *J* = 2 Hz, 1H), 8.35 (dd, *J* = 5, 1 Hz, 1H), 8.07 (m, 1H), 7.28 (dd, *J* = 8, 5 Hz, 1H), 4.83 (m, 1H), 4.11 (t, *J* = 9 Hz, 1H), 3.87 (dd, *J* = 9, 6 Hz, 1H), 3.72 (dd, *J* = 14, 4 Hz, 1H), 3.57 (dd, *J* = 14, 5 Hz, 1H).

Synthesis of triazole 209

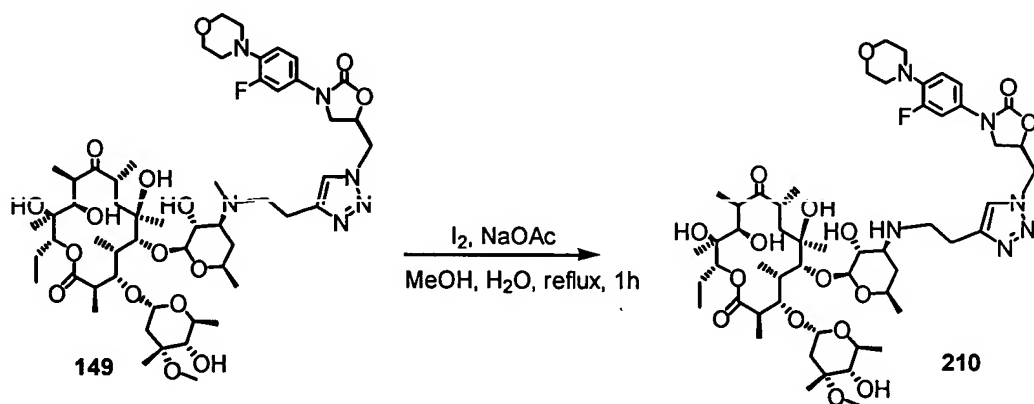
This compound was obtained from the reaction of alkyne **173** (0.17 g, 0.22 mmol) with azide **271** (0.080 g, 0.36 mmol) as described for triazole **206** above (Example 16) except that the

reaction was allowed to stir for 12 h. The crude was purified on silica gel, first eluting with CH₂Cl₂/MeOH 17:1, then with CH₂Cl₂/MeOH/NH₄OH 17:1:0.05 to 15:1:0.05 to 12:1:0.05 to 10:1:0.05 to give **209** as a white solid (0.117 g, 54%). Data for **209**: MS (ESI) *m/z* 1006.5 (M+H)⁺; ¹H-NMR (300 MHz, CDCl₃, partial): δ 8.67 (d, *J* = 3 Hz, 1H), 8.36 (dd, *J* = 5, 1 Hz, 1H), 7.84 (m, 1H), 7.62 (s, 1H), 7.28 (m, 1H), 5.16-5.05 (m, 2H), 4.75 (d, *J* = 4 Hz, 2H), 4.45 (d, *J* = 7 Hz, 1H), 3.64 (t, *J* = 7 Hz, 1H), 0.88 (m, 7H).

Example 19 – Synthesis of Triazole 210

Triazole **210** was synthesized by dealkylation of compound **149** (Scheme 45).

Scheme 45



Synthesis of triazole 210

Compound **149** (0.20 g, 0.183 mmol) and NaOAc (0.15 g, 1.83 mmol) were dissolved in 80% aqueous MeOH (5 mL), and the mixture was heated under gentle reflux for 1 h. The reaction was allowed to cool to room temperature and H₂O/NH₄OH 8: 1 (9 mL) was added. The mixture was extracted with CH₂Cl₂ (3 x 20 mL), the combined organic layer was extracted with H₂O/NH₄OH 5: 1 (20 mL), dried over Na₂SO₄ and the solvent evaporated. The crude was purified on silica gel eluting with CH₂Cl₂/MeOH/H₂O (containing a trace of NH₄OH) 20:1:0.05 to 18:1:0.05 to 15:1:0.05 to 12:1:0.05 to give **210** as a white solid (0.049 g). Data for **210**: MS (ESI) *m/z* 1079.4 (M+Na)⁺; ¹H-NMR (300 MHz, CDCl₃, partial): δ 7.55 (s, 1H), 7.25 (dd, *J* = 14, 2 Hz, 1H), 6.91 (dd, *J* = 9, 2 Hz, 1H), 6.82 (t, *J* = 9 Hz, 1H), 4.96 (m, 2H), 4.81 (d, *J* = 4 Hz, 1H), 4.64 (m, 2H), 4.31 (d, *J* = 7 Hz, 1H), 4.05 (t, *J* = 9 Hz, 1H), 3.47 (d, *J* = 7 Hz, 2H), 2.29-2.25 (m, 2H), 0.78 (t, *J* = 7 Hz, 3H).

Example 20 – Synthesis of Triazole 211

A solution of alkyne **198** (136 mg, 0.216 mmol) in tetrahydrofuran (3.0 mL) was treated with azide **158** (104 mg, 0.325 mmol), *i*-Pr₂NEt (1.1 mL, 6.58 mmol) and copper (I) iodide (82 mg, 0.432 mmol), and the mixture was stirred under argon at room temperature for 15 h. The reaction mixture was diluted with methylene chloride (50 mL), washed with saturated aqueous NH₄Cl (3 x 50 mL), and brine (2 x 50 mL). The organic phase was dried (Na₂SO₄), and evaporated. The residue was chromatographed on silica gel using a 4-10% gradient of methanol in methylene chloride as eluant to provide **211** as a white solid (0.112 g, 0.118 mmol, 56%).

Data for **211**: MS (ESI) *m/z* 949.3 (M+H)⁺; ¹HNMR (300 MHz, CDCl₃, partial): δ 7.68 (s, 1H), 7.33 (dd, *J* = 2, 14 Hz, 1H), 6.97 (dd, *J* = 2, 9 Hz, 1H), 6.89 (t, *J* = 9 Hz, 1H), 5.16 (dd, *J* = 3, 11 Hz, 1H), 5.09-4.99 (m, 1H), 4.72 (ddd, *J* = 4, 15, 18 Hz, 2H), 4.36 (d, *J* = 7 Hz, 1H), 4.13 (t, *J* = 9 Hz, 2H), 0.83 (t, *J* = 7 Hz, 3H).

Example 21 – Synthesis of Triazole 212

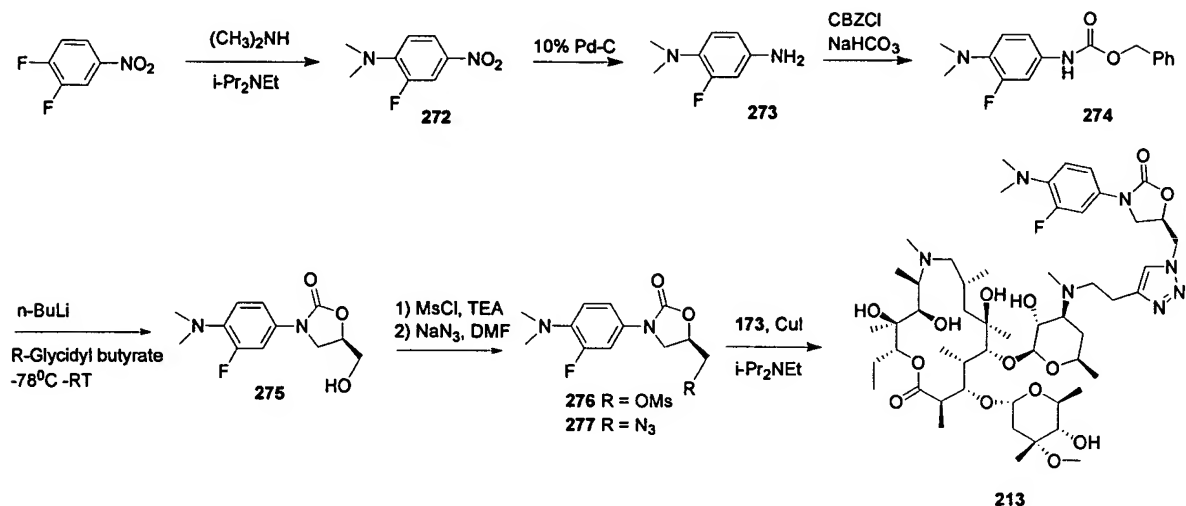
To a mixture of alkyne **201** (48 mg, 0.076 mmol), azide **189** (19.9 mg, 0.084 mmol) and copper (I) iodide (8 mg, 0.038 mmol) was added THF (3 mL) and the mixture was repeatedly degassed and flushed with argon. Then *i*-Pr₂NEt (0.1 mL) was introduced and the mixture was stirred at room temperature for 1 h. The reaction mixture was poured into NH₄Cl (30 mL) and stirred for few minutes. Then NH₄OH (3 mL) was added and the mixture was extracted with methylene chloride (3 x 40 mL). The combined organic layers were dried (Na₂SO₄), concentrated and flash chromatographed over silica gel (methylene chloride: MeOH : NH₄OH = 48:2:0.05) to provide **212** (55 mg, 0.06 mmol, 79%). Data for **212**: MS (ESI) *m/z* 862.3 (M+H)⁺; ¹HNMR (300 MHz, CDCl₃, partial): δ 7.60 (s, 1H), 7.32 (m, 1H), 7.09 (dd, *J* = 3, 9 Hz, 1H), 6.85 (brt, 1H), 0.86 (t, *J* = 7 Hz, 3H).

Example 22 – Synthesis of Triazole 213

Scheme 46 illustrates the synthesis of triazole **213**. 3,4-Difluoronitrobenzene is converted to nitroaniline **272** via an aromatic substitution reaction. The nitro group of **272** is reduced to afford aniline **273** which is transformed to carbamate **274**. Oxazolidinone formation

to provide **275** is followed by conversion to the azide to yield **277**. Cycloaddition of azide **277** with alkyne **173** afforded triazole **213**.

Scheme 46



5

Synthesis of nitroaniline **272**

3, 4-Difluoronitrobenzene (3 mL, 27.1 mmol) was added to a solution of dimethyl amine (15 mL, 29.8 mmol) and *i*-Pr₂NEt (5.2 mL, 29.8 mmol) in ethyl acetate (20 mL) at 0°C and the mixture was stirred at room temperature overnight. The yellow solution was concentrated and redissolved in methylene chloride (100 mL) and then washed with water (50 mL). The aqueous layer was basified with KOH pellets and back extracted with methylene chloride (2 x 50 mL). The combined organic layer after evaporation afforded a yellow solid which was dissolved in 6N HCl (60 mL) at 0°C and washed with methylene chloride (3 x 60 mL). The solution was basified with KOH pellets (pH 10) and extracted with methylene chloride (3 x 100 mL). The combined organic phase was dried (Na₂SO₄) and concentrated to provide **272** (1.8 g). Data for **272**:
¹HNMR (300 MHz, CDCl₃): δ 7.95 (dd, *J* = 2, 8 Hz, 1H), 7.88 (dd, *J* = 3, 14 Hz, 1H), 6.72 (t, *J* = 9 Hz, 1H), 3.10 (s, 6H).

15

Synthesis of aniline **273**

20

To a solution of nitroaniline **272** (1.7 g, 9.2 mmol) in EtOH and THF (2:1, 30 mL) was added 10% Pd-C (0.2 g) and the mixture was stirred overnight at room temperature under hydrogen atmosphere. It was filtered through a Whatman filter paper and the residue was washed with methylene chloride (4 x 25 mL). The combined organic layer was evaporated to

provide **273** (1.3 g). Data for **273**: ¹HNMR (300 MHz, CDCl₃): δ 6.81 (t, *J* = 11 Hz, 1H), 6.46-6.37 (m, 2H), 2.73 (s, 6H).

Synthesis of carbamate **274**

5 To a solution of aniline **273** (1.3 g, 8.4 mmol) in a mixture of acetone (20 mL) and water (5 mL) was added NaHCO₃ (1.76 g, 21 mmol) at 0°C and the mixture was stirred for few minutes. Then benzyl chloroformate (1.5 mL, 10.1 mmol) was added dropwise and the mixture was stirred at 0°C for 1 h. The reaction mixture was concentrated and dissolved in methylene chloride (50 mL). The organic layer was washed with brine (3 x 50 mL), dried (Na₂SO₄) and
10 concentrated to provide **274** (2.4 g) of suitable purity for use in subsequent reactions. Data for **274**: ¹HNMR (300 MHz, CDCl₃): δ 7.38-7.12 (m, 6H), 6.95 (brd, *J* = 8 Hz, 1H), 6.84 (t, *J* = 9 Hz, 1H), 6.57 (brs, 1H), 5.18 (s, 2H), 2.78 (s, 6H).

Synthesis of oxazolidinone **275**

15 To a solution of carbamate **274** (2.4 g, 8.3 mmol) in THF (80 mL) was added n-BuLi (4.32 mL, 2.5 M in hexane, 10.79 mmol) at -78°C and the mixture was stirred for 1 h. (*R*)-Glycidyl butyrate (1.5 mL, 10.87 mmol) was added and the reaction warmed to room temperature and allowed to stir overnight. The reaction was carefully poured into saturated NH₄Cl (70 mL) and extracted with EtOAc (3 x 100 mL). The combined organic layers were
20 washed with brine (1 x 200 mL), dried (Na₂SO₄) and concentrated. Flash chromatography over silica gel (60%-100% EtOAc in hexanes) provided **275** (2 g) **275** as a white solid. Data for **275**: ¹HNMR (300 MHz, CDCl₃): δ 7.38 (dd, *J* = 3, 15 Hz, 1H), 7.10 (dd, *J* = 3, 9 Hz 1H), 6.88 (t, *J* = 12 Hz, 1H), 4.75-4.71 (m, 1H), 4.02-3.93 (m, 3H), 3.79-3.75 (m, 1H), 2.81 (s, 6H).

25 Synthesis of azide **277**

To alcohol **275** (900 mg, 3.54 mmol) in methylene chloride (35 mL) at 0°C was added triethylamine (0.5 mL, 3.58 mmol) and methanesulfonyl chloride (0.41 mL, 5.31 mmol). After stirring for 1 h at 0°C, the reaction was poured into water (100 mL) and extracted with methylene chloride (3 x 100 mL). The combined organic layers were washed with water (2 x 100 mL),
30 dried (Na₂SO₄) and concentrated to yield 1.1 g of pure product **276**. To a solution of mesylate **276** (1.1 g, 3.3 mmol) in DMF (15 mL) was added sodium azide (646 mg, 9.9 mmol) and the

reaction was heated at 75°C overnight. The reaction was poured into water (100 mL) and extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with water (3 x 100 mL), dried (Na₂SO₄) and concentrated to provide a solid. The material was further purified by flash chromatography over silica gel (50% EtOAc in hexanes) to yield 858 mg of pure azide **277**. Data for **277**: ¹HNMR (300 MHz, CDCl₃): δ 7.38 (dd, *J* = 3, 15 Hz, 1H), 7.10 (dd, *J* = 3, 9 Hz, 1H), 6.89 (t, *J* = 9 Hz, 1H), 4.78-4.75 (m, 1H), 4.01 (t, *J* = 9 Hz, 1H), 3.81 (dd, *J* = 6, 9 Hz, 1H), 3.69 (dd, *J* = 5, 13 Hz, 1H), 3.58 (dd, *J* = 5, 13 Hz, 1H), 2.82 (s, 3H).

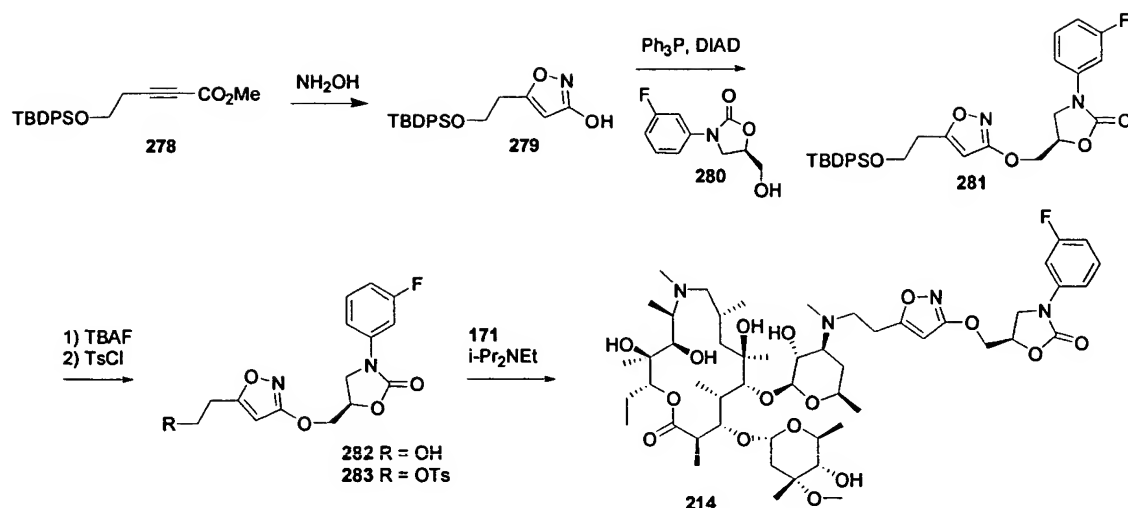
Synthesis of triazole **213**

To a mixture of alkyne **173** (200 mg, 0.254 mmol), azide **277** (85 mg, 0.305 mmol) and copper (I) iodide (24 mg, 0.127 mmol) was added THF (10 mL) and the mixture was repeatedly degassed and flushed with argon. Then *i*-Pr₂NEt (0.1 mL) was introduced and the mixture was stirred at room temperature for 1 h. The reaction mixture was poured into NH₄Cl (30 mL) and stirred for few minutes. Then NH₄OH (3 mL) was added and the mixture extracted with methylene chloride (3 x 40 mL). The combined organic layers were dried (Na₂SO₄), concentrated and flash chromatographed over silica gel (methylene chloride: MeOH:NH₄OH = 12:1;0.05) to provide 223 mg of triazole **213**. Data for **213**: MS (ESI) *m/z* 1066.5 (M+H)⁺; ¹HNMR (300 MHz, CDCl₃, partial): δ 7.63 (s, 1H), 7.27 (dd, *J* = 2, 8 Hz, 1H), 6.94 (dd, *J* = 2, 9 Hz, 1H), 6.84 (t, *J* = 9 Hz, 1H), 5.30-5.04 (m, 2H), 0.89 (t, *J* = 7 Hz, 3H).

Example 23 – Synthesis of Isoxazole **214**

Scheme 47 exemplifies the synthesis of isoxazole **214**. Known alkyne **278** (Zacharie, B. *et al. J. Med. Chem.* 1997, 40, 2883) was converted by hydroxylamine to hydroxyisoxazole **279**. The Mitsunobu reaction of **279** with alcohol **280** (synthesized from 3-fluoroaniline using the chemistry reported in the literature (Brickner, S.J. *et al. J. Med. Chem.* 1996, 39, 673)) afforded isoxazole **281**. Desilylation of **281** afforded alcohol **282** which was subsequently converted to tosylate **283**. Alkylation of amine **171** with tosylate **283** yielded isoxazole **214**.

Scheme 47



Synthesis of hydroxyisoxazole **279**

To a solution of hydroxylamine hydrochloride (208 mg, 3.0 mmol) in MeOH (5 mL) was added 10% NaOH (3.14 mL, 7.85 mmol) solution followed by a solution of alkyne **278** (900 mg, 2.5 mmol) in MeOH (1.5 mL). The mixture was stirred overnight at room temperature and was then acidified with 6N HCl (pH 2), saturated with sodium sulphate. The mixture was extracted with diethyl ether (3 x 50 mL). The combined organic layers were washed with water (3 x 100 mL), dried (Na₂SO₄), concentrated and chromatographed over silica gel (20% EtOAc in hexanes) to provide 280 mg pure isoxazole **279** as a white solid. Data for **279**: MS (ESI) *m/z* 408.9 (M+CH₃CN)⁺; ¹HNMR (300 MHz, CDCl₃): δ 7.62 (brd, 4H), 7.46-7.35 (m, 6H), 5.76 (s, 1H), 3.91 (t, *J* = 6 Hz, 2H), 2.86 (t, *J* = 7 Hz, 2H), 1.03 (s, 9H).

Synthesis of isoxazole **281**

To a solution of isoxazole **279** (100 mg, .272 mmol), alcohol **280** (86 mg, 0.408 mmol) and triphenyl phosphine (114 mg, 0.435 mmol) in THF (8 mL) was added diisopropyl azodicarboxylate (0.08 mL, 0.408 mmol) at -20°C. The solution was warmed to room temperature and stirred for 3 h. The mixture was concentrated and chromatographed over silica gel (25-30% EtOAc in hexanes) to provide 140 mg of **281**. Data for **281**: MS (ESI) *m/z* 583.0 (M+Na)⁺; ¹HNMR (300 MHz, CDCl₃): δ 7.61 (dd, *J* = 3, 9 Hz, 4H), 7.48-7.32 (m, 9H), 6.85 (brt, 1H), 5.72 (s, 1H), 5.02-4.94 (m, 1H), 4.53 (dd, *J* = 4, 12 Hz, 1H), 4.46 (dd, *J* = 5, 12 Hz, 1H), 4.16-4.09 (m, 2H), 3.93 (t, *J* = 6 Hz, 2H), 2.87 (t, *J* = 6 Hz, 2H), 1.03 (s, 9H).

Synthesis of isoxazole 282

To a solution of silyl ether **281** (140 mg, 0.25 mmol) in THF (5 mL) was added tetrabutylammonium fluoride (0.5 mL, 1M in THF) at 0°C and the mixture was stirred overnight at room temperature. The reaction mixture was concentrated and dissolved in EtOAc (50 mL).

- 5 The organic layer was washed with brine (2 x 50 mL), dried (Na₂SO₄), concentrated and chromatographed over silica gel (70% EtOAc in hexanes) to provide 70 mg of **282**. Data for **282**: MS (ESI) m/z 322.8 (M+H)⁺; ¹HNMR (300 MHz, CDCl₃): δ 7.45 (ddd, J = 2, 5, 11 Hz, 1H), 7.30-7.21 (m, 2H), 6.88-6.82 (m, 1H), 5.78 (s, 1H), 5.04-4.96 (m, 1H), 4.52 (dd, J = 4, 12 Hz, 1H), 4.43 (dd, J = 5, 11 Hz, 1H), 4.15 (t, J = 9 Hz, 1H), 3.96 (dd, J = 6, 9 Hz, 1H), 3.91 (t, J = 6 Hz, 2H), 2.91 (t, J = 6 Hz).

Synthesis of tosylate 283

- p-Toluenesulfonyl chloride (71.5 mg, 0.375 mmol) was added to a solution of isoxazole **282** (60 mg, 0.187 mmol), triethylamine (0.065 mL, 0.468 mmol) and DMAP (cat.) in methylene chloride (5 mL) at 0°C. The mixture was then allowed to stir at room temperature for 4 h. The reaction mixture was diluted with EtOAc (30 mL) and washed with brine (3 x 30 mL), dried (Na₂SO₄), concentrated and chromatographed over silica gel (50% EtOAc in hexanes) to yield 77.6 mg of pure tosylate **283**. Data for **283**: MS (ESI) m/z 476.9 (M+H)⁺, 498.9 (M+Na)⁺; ¹HNMR (300 MHz, CDCl₃): δ 7.76 (d, J = 9 Hz, 2H), 7.46 (ddd, J = 2, 5, 11 Hz, 1H), 7.38-7.23 (m, 4H), 6.89-6.83 (m, 1H), 5.73 (s, 1H), 5.04-4.96 (m, 1H), 4.52 (dd, J = 4, 12 Hz, 1H), 4.44 (dd, J = 5, 11 Hz, 1H), 4.26 (t, J = 6 Hz, 2H), 4.16 (t, J = 9 Hz, 1H), 3.96 (dd, J = 6, 9 Hz, 1H), 3.02 (t, J = 6 Hz, 2H), 2.45 (s, 3H).

Synthesis of isoxazole 214

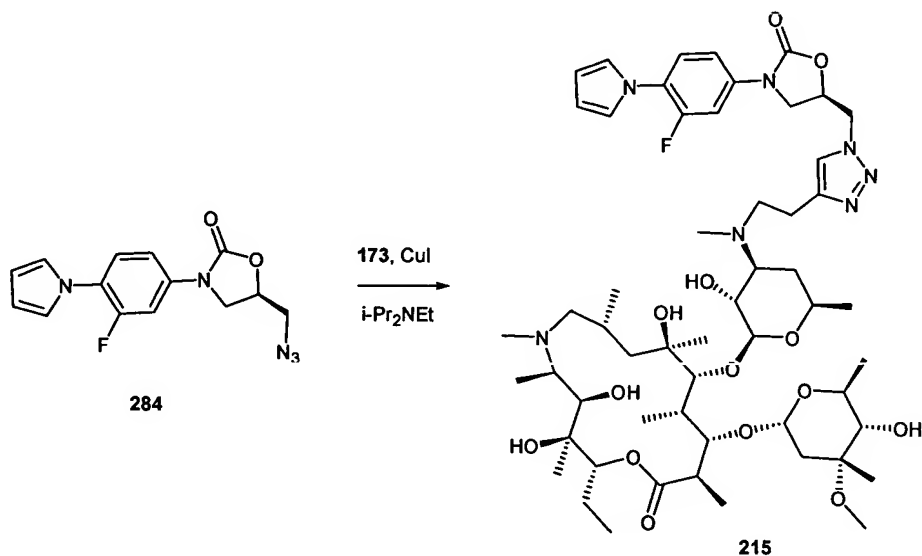
- 25 A suspension of *N*-desmethylazithromycin **171** (100 mg, 0.136 mmol), tosylate **283** (52 mg, 0.109 mmol), i-Pr₂NEt (3 mL) and NaI (cat.) in THF (4 mL) was heated to reflux for 72h. The reaction mixture was concentrated and chromatographed over silica gel (methylene chloride:MeOH:NH₄OH = 12:1:0.01) to yield 7 mg of **214**. Data for **214**: MS (ESI) m/z 1039.1 (M+H)⁺, 1061.5 (M+Na)⁺; ¹HNMR (300 MHz, CDCl₃, partial): δ 7.46 (ddd, J = 2, 5, 11 Hz, 1H), 7.38-7.23 (m, 2H), 6.86 (brt, 1H), 5.72 (s, 1H), 5.08 (d, J = 5 Hz, 1H), 5.02-4.96 (m, 1H),
- 30

4.68 (d, $J = 8$ Hz, 1H), 4.53 (dd, $J = 4, 11$ Hz, 1H), 4.46 (dd, $J = 5, 9$ Hz, 1H), 0.90 (t, $J = 6$ Hz, 3H).

Example 24 – Synthesis of triazole 215

5 Scheme 48 exemplifies the synthesis of triazole **215**. The cycloaddition of known azide **284** (see US Patent No. 6,124,334) and alkyne **173** afforded triazole **215**.

Scheme 48



10

Synthesis of triazole 215

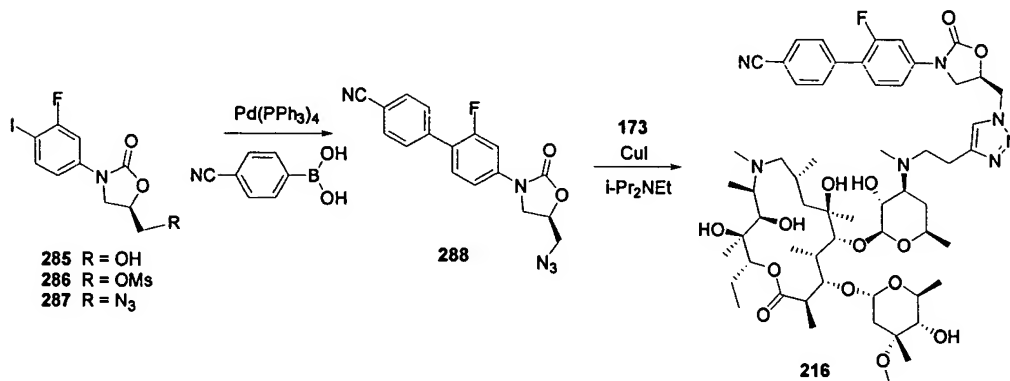
A solution of alkyne **173** (0.100 g, 0.13 mmol) and azide **284** (0.046 g, 0.19 mmol) in tetrahydrofuran (1.3 mL) was treated with *N,N*-diisopropylethylamine (0.670 mL, 3.8 mmol) and copper (I) iodide (36 mg, 0.19 mmol) and the mixture was stirred under argon at 23°C for 2.5 h.

15 The reaction mixture was diluted with saturated aqueous ammonium hydroxide (10 mL) and extracted with dichloromethane (4×30 mL). The combined organic fractions were dried (Na_2SO_4), evaporated, and the residue purified by flash chromatography (SiO_2 , ammonium hydroxide/methanol/dichloromethane 0.05:1:9) to provide **215** (53 mg, 0.048 mmol, 38%) as a white powder. Data for **215**: MS (ESI) m/z 545.0 ($\text{M}+2\text{H}$) $^{2+}$; ^1H NMR (300 MHz, CDCl_3 ,
20 partial): δ 7.81 (s, 1H), 7.61–7.54 (m, 1H), 7.39–7.33 (m, 1H), 7.21–7.15 (m, 1H), 6.99 (d, $J = 2$ Hz, 2H), 6.34 (d, $J = 1$ Hz, 2H), 3.29 (s, 3H), 3.26 (s, 3H), 0.89–0.78 (m, 6H).

Example 25 – Synthesis of triazole 216

Scheme 49 depicts the synthesis of triazole **216**. The known alcohol **285** (see International Patent Application WO0306440) is converted by standard chemistry to azide **287**. This azide is coupled to 4-cyanophenylboronic acid using the Suzuki reaction to afford biaryl azide **288**. Cycloaddition of **288** with alkyne **173** afforded triazole **216**.

Scheme 49



10 Synthesis of mesylate **286**

A solution of alcohol **285** (2.5 g, 7.4 mmol) in methylene chloride (40 mL) was cooled to 0 °C under argon and treated with Et₃N (1.80 mL, 13.2 mmol) and methanesulfonyl chloride (0.57 mL, 7.4 mmol). The reaction mixture was warmed to 23°C for 0.5 h then washed with 1 M hydrochloric acid (50 mL), saturated aqueous sodium bicarbonate (50 mL) and saturated aqueous sodium chloride (50 mL). Drying (Na₂SO₄) and evaporation provided mesylate **286** (2.8 g, 6.7 mmol, 91%) as a white powder. Data for **286**: ¹HNMR (300 MHz, DMSO-*d*₆): δ 7.85 (dd, *J* = 9, 8 Hz, 1H), 7.57 (dd, *J* = 11, 2 Hz, 1H), 7.22 (dd, *J* = 9, 2 Hz, 1H), 5.07–5.00 (m, 1H), 4.53–4.48 (m, 2H), 4.22–4.19 (m, 1H), 3.83 (dd, *J* = 9, 6 Hz, 1H), 3.26 (s, 3 H).

20 Synthesis of azide **287**

A solution of mesylate **286** (7.00 g, 16.8 mmol) in dimethylformamide (50 mL) was treated with sodium azide (1.5 g, 23 mmol) and stirred at 50°C under argon for 18 h. The reaction mixture was cooled to 20°C, poured into H₂O (400 mL) and stirred at 0°C. The resulting precipitate was filtered, washed with H₂O and dried under reduced pressure to provide azide **287** as a white powder (4.0 g, 11 mmol, 66%). Data for **287**: ¹HNMR (300 MHz, CDCl₃): δ 7.71

(dd, $J = 9$, 7 Hz, 1H), 7.48 (dd, $J = 10$, 2 Hz, 1H), 7.06 (dd, $J = 9$, 2 Hz, 1H), 4.89–4.77 (m, 1H), 4.09–4.04 (m, 1H), 3.84 (dd, $J = 9$, 6 Hz, 1H), 3.73 (dd, $J = 13$, 5 Hz, 1H), 3.61 (dd, $J = 13$, 5 Hz, 1H).

5 Synthesis of azide **288**

A solution of azide **287** (0.36 g, 1.0 mmol) in toluene/ethanol/H₂O (3:1:1, 10 mL) was treated with potassium carbonate (0.41 g, 3.0 mmol), 4-cyanophenylboronic acid (0.18 g, 1.2 mmol) and tetrakis(triphenylphosphine)palladium (0.005 g, 0.05 mmol), and the mixture was stirred under argon at 80°C for 0.5 h. The reaction mixture was cooled to room temperature, diluted with ethyl acetate (50 mL), washed with H₂O (3 × 50 mL), dried (Na₂SO₄), and evaporated. Flash chromatography (SiO₂, hexanes/ethyl acetate 1:1) provided azide **288** (0.23 g, 0.67 mmol, 67%) as a white powder. Data for **288**: ¹HNMR (300 MHz, CDCl₃): δ 7.72–7.69 (m, 2H), 7.64–7.60 (m, 2H), 7.55 (dd, $J = 13$, 2 Hz), 7.46–7.41 (m, 1H), 7.35 (dd, $J = 9$, 2 Hz), 4.87–4.78 (m, 1H), 4.14–4.08 (m, 1H), 3.89 (dd, $J = 9$, 6 Hz, 1H), 3.73 (dd, $J = 13$, 5 Hz, 1H), 3.61 (dd, $J = 13$, 5 Hz, 1H).

Synthesis of triazole **216**

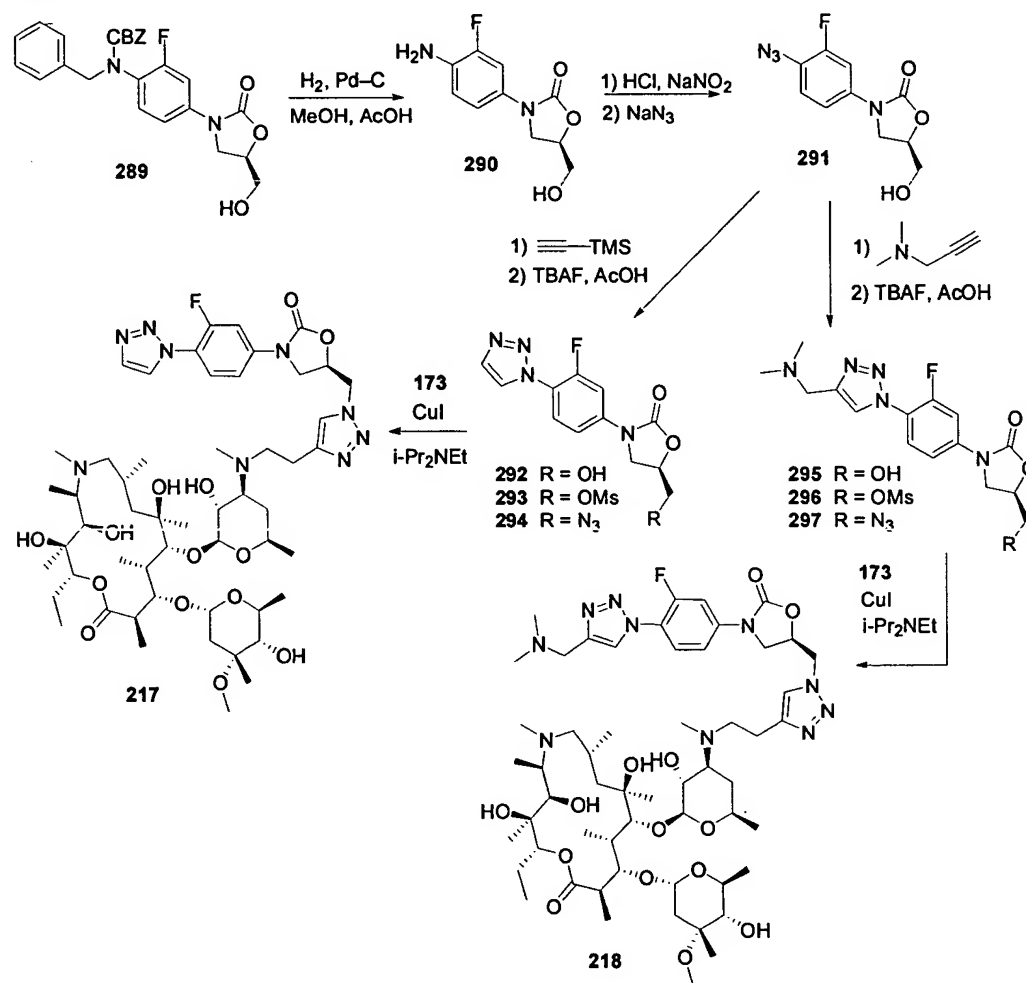
A solution of alkyne **173** (0.19 g, 0.24 mmol) and azide **288** (0.10 g, 0.30 mmol) in tetrahydrofuran (5.0 mL) was treated with *N,N*-diisopropylethylamine (0.042 mL, 0.24 mmol) and copper (I) iodide (19 mg, 0.10 mmol) and the mixture was stirred under argon at 23°C for 0.5 h. The reaction mixture was diluted with saturated aqueous ammonium hydroxide (10 mL) and extracted with dichloromethane (3 × 30 mL). The combined organic fractions were dried (Na₂SO₄) and evaporated, and the residue purified by flash chromatography (SiO₂, ammonium hydroxide/methanol/dichloromethane (0.05:1:9) to provide **216** (110 mg, 0.098 mmol, 41%) as a white powder. Data for **216**: MS (ESI) m/z 1125 (M+H)⁺; ¹HNMR (300 MHz, CDCl₃, partial): δ 7.72–7.69 (m, 2H), 7.62 (s, 1H), 7.60 (m, 2H), 7.49–7.44 (m, 1H), 7.42–7.37 (m, 1H), 7.22–7.19 (m, 1H), 3.31 (s, 3H), 2.34 (s, 3H), 2.30 (s, 3H), 0.88–0.86 (m, 6H).

Example 26 – Synthesis of triazoles **217** and **218**

Scheme 50 details the synthesis of triazoles **217** and **218**. The known carbamate **289** (see *J. Med. Chem.* 2000, 43, 953) was deprotected to afford aniline **290**. Diazotization of **290**

afforded azide **291**, which was subsequently converted by cycloaddition chemistry with available alkynes to triazoles **292** and **295**. Manipulation of these intermediates to azides **294** and **297** was followed by cycloaddition with alkyne **173** to afford triazoles **217** and **218** respectively.

5 Scheme 50



Synthesis of aniline **290**

A solution of carbamate **289** (3.6 g, 7.9 mmol) in methanol (120 mL) was treated with acetic acid (30 mL) and 10% Pd-C (1.0 g) and the mixture was stirred under a balloon of hydrogen for 12 h at 23°C. The reaction mixture was filtered through a plug of SiO_2 and evaporated under reduced pressure, providing **290** (1.5 g, 6.6 mmol, 84%) as a pink-white solid. Data for **290**: ^1H NMR (300 MHz, $\text{DMSO}-d_6$): δ 7.32 (dd, $J = 14, 3$, Hz, 1H), 6.99–6.95 (m, 1H),

6.75 (dd, $J = 10$, 9 Hz, 1H), 4.99 (s, 2H), 4.66–4.58 (m, 1H), 4.01–3.94 (m, 1H), 3.72 (dd, $J = 9$, 6 Hz, 1H), 3.63 (dd, $J = 12$, 4 Hz, 1H), 3.50 (dd, $J = 12$, 4 Hz, 1H).

Synthesis of azide **291**

5 A suspension of aniline **290** (0.56 g, 2.5 mmol) in H₂O (10 mL) was cooled to 0 °C and treated with concentrated hydrochloric acid (1.0 mL, 12.4 mmol) and sodium nitrite (0.19 g, 2.8 mmol). A solution of sodium azide (0.24 g, 3.8 mmol) in H₂O (1.0 mL) was added after 1 h, and stirring at 0°C was continued for an additional 1 h. The reaction mixture was diluted with saturated aqueous sodium bicarbonate (20 mL) and extracted with ethyl acetate (100 mL). The
10 organic fraction was washed with H₂O (100 mL) dried (Na₂SO₄) and evaporated to an orange film. Data for **291**: ¹HNMR (300 MHz, CD₃OD): δ 7.51 (dd, $J = 14$, 3 Hz, 1H), 7.19 (m, 1H), 7.03 (m, 1H), 4.70–4.61 (m, 1H), 4.02–3.96 (m, 1H), 3.79 (m, 1H), 3.74 (m, 1H).

Synthesis of triazole **292**

15 A solution of azide **291** (0.14 g, 0.56 mmol) and trimethylsilylacetylene (0.47 mL, 3.3 mmol) in dimethylformamide (4 mL) was stirred at 60°C for 16 h. The reaction mixture was cooled to 23°C, concentrated under reduced pressure to a volume of 2.0 mL, and treated with tetrabutylammonium fluoride (1.5 mL of a 1.0 M solution in tetrahydrofuran) and acetic acid (0.1 mL) and the mixture was stirred for 12 h. Ethyl acetate (100 mL) was added and the solution
20 was washed with H₂O (3 \times 75 mL), dried (Na₂SO₄) and evaporated to provide **292** (87 mg, 0.31 mmol, 56%) as a brown foam that was used directly in the next step.

Synthesis of azide **294**

25 A solution of alcohol **292** (94 mg, 0.34 mmol) in dichloromethane (3.5 mL) was cooled to 0°C and treated with triethylamine (0.095 mL, 0.68 mmol) and methanesulfonyl chloride (0.029 mL, 0.37 mmol). The reaction mixture was stirred at 23°C for 1 h, then diluted with ethyl acetate (150 mL) and washed with 1 M hydrochloric acid (2 \times 75 mL), 10% aqueous sodium carbonate (75 mL), dried (Na₂SO₄), and evaporated. Flash chromatography (SiO₂, 50–100% ethyl acetate/hexanes) provided mesylate **293** (50 mg, 0.14 mmol, 41%) as a yellow film. Data
30 for **293**: MS (ESI) m/z 357 (M+H)⁺; ¹HNMR (300 MHz, CDCl₃): δ 8.11–8.09 (m, 1H), 8.04–7.98 (m, 1H), 7.88 (m, 1H), 7.85 (dd, $J = 13$, 2 Hz, 1H), 7.32–7.27 (m, 1H), 5.04–4.96 (m, 1H),

4.54 (dd, $J = 12$, 4 Hz, 1H), 4.47 (dd, $J = 12$, 4 Hz, 1H), 4.26–4.20 (m, 1H), 4.03 (dd, $J = 9$, 6 Hz, 1H), 3.12 (s, 3H), 2.36 (s, 6H).

A solution of mesylate **293** (0.050 g, 0.15 mmol) in dimethylformamide (1.5 mL) was treated with sodium azide (0.018 g, 0.28 mmol) and stirred at 60°C under argon for 12 h. The reaction mixture was cooled to 20 °C, diluted with ethyl acetate (75 mL), washed with H₂O (3 × 50 mL), dried (Na₂SO₄), and evaporated under reduced pressure providing azide **294** as a yellow film (41 mg).

Synthesis of triazole **217**

A solution of crude azide **294** obtained above (0.038 g, 0.13 mmol) and alkyne **173** (0.079 g, 0.10 mmol) in tetrahydrofuran (5.0 mL) was treated with diisopropylethylamine (0.050 mL, 0.29 mmol) and copper (I) iodide (18 mg, 0.094 mmol) and stirred under argon at 23°C for 1 h. The reaction mixture was diluted with saturated aqueous ammonium hydroxide (10 mL) and extracted with dichloromethane (3 × 30 mL). The combined organic fractions were dried (Na₂SO₄), evaporated, and the residue purified by flash chromatography (SiO₂, ammonium hydroxide/methanol/dichloromethane (0.05:1:9) to provide triazole **217** (32 mg, 0.029 mmol, 29%) as a yellow foam. Data for **217**: MS (ESI) m/z 546 ($M+2H$)²⁺; ¹HNMR (300 MHz, CDCl₃, partial): δ 8.01 (d, $J = 1$ Hz, 1H), 7.88–7.83 (m, 1H), 7.79 (d, $J = 1$ Hz, 1H), 7.68 (s, 1H), 7.60 (m, 1H), 7.20 (m, 1H), 3.26 (s, 3H), 2.30 (s, 3H), 2.22 (s, 3H), 0.88–0.84 (m, 6H).

Synthesis of triazole **295**

A solution of azide **291** (0.14 g, 0.56 mmol) and *N,N*-dimethylpropargylamine (0.30 mL, 2.6 mmol) in dimethylformamide (4 mL) was treated with copper (I) iodide (0.030 g, 0.16 mmol) and stirred at 20°C for 1 h. The reaction mixture was diluted with ethyl acetate (100 mL) and washed with 10% ammonium hydroxide (2 × 100 mL) and saturated aqueous sodium chloride (100 mL), dried (Na₂SO₄) and evaporated. Flash chromatography of the crude material (SiO₂, ammonium hydroxide/methanol/dichloromethane (0.05:1:9) provided triazole **295** (18 mg, 0.054 mmol, 9.6%) as a yellow film. Data for **295**: ¹HNMR (300 MHz, CDCl₃): δ 8.02–8.01 (m, 1H), 7.86–7.81 (m, 1H), 7.71 (dd, $J = 14$, 2 Hz, 1H), 7.33–7.27 (m, 1H), 4.83–4.76 (m, 1H), 4.15–4.04 (m, 2H), 4.02 (dd, $J = 9$, 4 Hz, 1H), 3.78 (dd, $J = 13$, 3 Hz, 1H), 3.73–3.71 (m, 2H), 2.36 (s, 6H).

Synthesis of azide **297**

A solution of alcohol **295** (17 mg, 0.050 mmol) in dichloromethane (0.5 mL) was cooled to 0°C and treated with triethylamine (0.014 mL, 0.10 mmol) and methanesulfonyl chloride (0.0043 mL, 0.056 mmol). The reaction mixture was stirred at 23°C for 1 h, then diluted with ethyl acetate (100 mL) and washed with 10% aqueous sodium carbonate (2 × 100 mL), dried (Na₂SO₄) and evaporated. Flash chromatography (SiO₂, ammonium hydroxide/methanol/dichloromethane (0.05:1:9) provided mesylate **296** (17 mg, 0.041 mmol, 82%) as a yellow film. Data for **296**: MS (ESI) *m/z* 414 (M+H)⁺; ¹HNMR (300 MHz, CDCl₃): δ 8.02–8.01 (m, 1H), 8.05–7.95 (m, 1H), 7.83 (dd, *J* = 13, 2 Hz, 1H), 7.31–7.27 (m, 1H), 5.04–4.97 (m, 1H), 4.54 (dd, *J* = 12, 4 Hz, 1H), 4.47 (dd, *J* = 12, 4 Hz, 1H), 4.03 (dd, *J* = 9, 6 Hz, 1H), 3.70 (s, 2H), 3.12 (s, 3H), 2.36 (s, 6H).

A solution of the above mesylate **296** (0.017 g, 0.042 mmol) in dimethylformamide (0.40 mL) was treated with sodium azide (0.006 g, 0.848 mmol) and stirred at 60°C under argon for 12 h. The reaction mixture was cooled to 20°C, diluted with ethyl acetate (75 mL), washed with H₂O (3 × 50 mL), dried (Na₂SO₄), and evaporated under reduced pressure providing azide **297** as a white foam (15 mg).

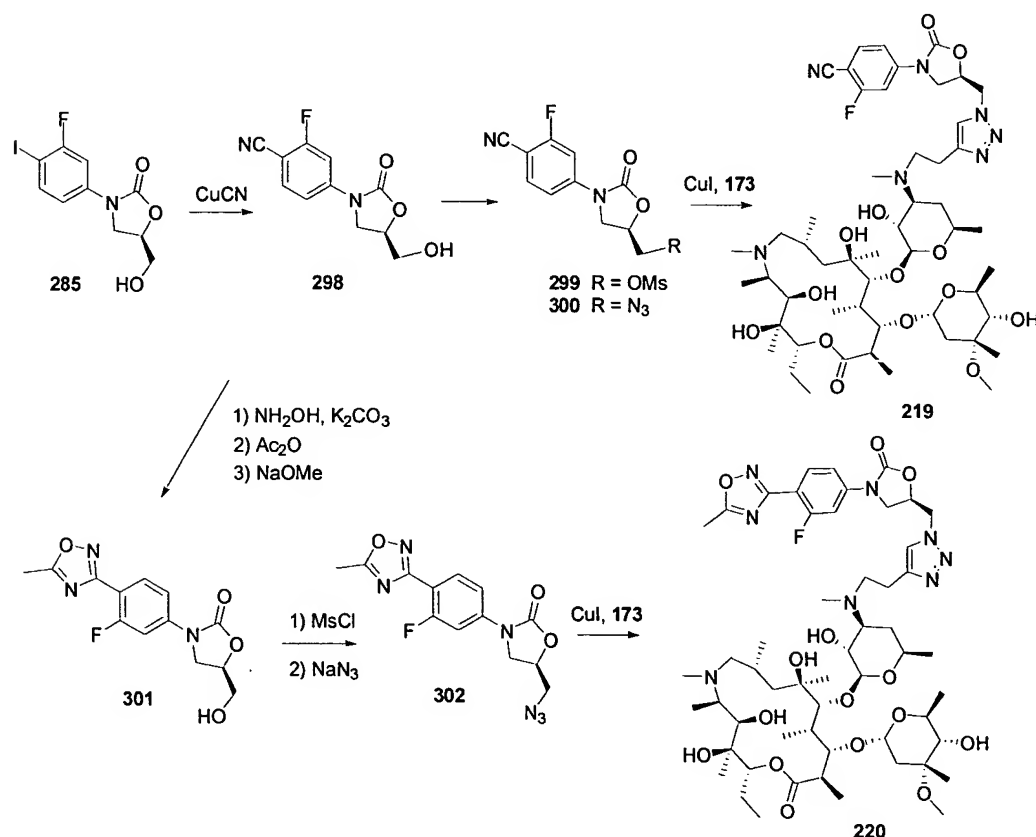
Synthesis of triazole **218**

A solution of crude azide **297** (0.012 g, 0.033 mmol) and alkyne **173** (0.021 g, 0.027 mmol) in tetrahydrofuran (1.4 mL) was treated with diisopropylethylamine (0.014 mL, 0.13 mmol) and copper (I) iodide (4.7 mg, 0.025 mmol) and stirred under argon at 23°C for 1 h. The reaction mixture was diluted with saturated aqueous ammonium hydroxide (10 mL) and extracted with dichloromethane (3 × 30 mL). The combined organic fractions were dried (Na₂SO₄), evaporated, and the residue purified by flash chromatography (SiO₂, ammonium hydroxide/methanol/dichloromethane (0.05:1:9) to provide triazole **218** (12 mg, 0.010 mmol, 39%) as a yellow foam. Data for **218**: MS (ESI) *m/z* 574 (M+2H)²⁺; ¹HNMR (300 MHz, CDCl₃, partial): δ 8.11 (m, 1H), 7.89–7.84 (m, 1H), 7.67 (s, 1H), 7.58 (m, 1H), 7.20 (m, 1H), 3.22 (s, 3H), 2.38 (s, 6H), 2.31 (s, 3H), 2.23 (s, 3H), 0.88–0.84 (m, 6H).

Example 27 – Synthesis of triazoles 219 and 220

Scheme 51 details the synthesis of triazoles **219** and **220**. Iodoaryl alcohol **285** is converted to nitrile **298** which is then transformed to azide **300** via mesylate **299**. Cycloaddition of azide **300** and alkyne **173** yielded triazole **219**. Nitrile **298** was manipulated to oxadiazole **301**, which served as the precursor to azide **302**. Cycloaddition of **302** with **173** afforded triazole **220**.

Scheme 51



10

Synthesis of nitrile 298

A solution of alcohol **285** (5.4g, 16.1 mmol) in dimethylformamide (16 mL) was treated with copper (I) cyanide (1.60 g, 17.7 mmol) and stirred at 145°C under argon for 18 h. The reaction mixture was cooled to 23°C and diluted with methylene chloride (100 mL), and washed with saturated aqueous ammonium chloride (100 mL) and saturated aqueous sodium chloride (100 mL). Drying (Na_2SO_4) and evaporation provided **298** (2.9 g, 12.3 mmol, 76%) as a white powder. Data for **298**: ^1H NMR (300 MHz, CD_3OD): δ 7.68 (dd, $J = 12, 2$ Hz, 1H), 7.62 (dd, $J =$

9, 8 Hz, 1H), 7.39 (dd, $J = 9$, 2 Hz, 1H), 4.71–4.65 (m, 1H), 4.08–4.02 (m, 1H), 3.86 (dd, $J = 9$, 6 Hz, 1H), 3.77 (dd, $J = 13$, 3 Hz, 1H), 3.60 (dd, $J = 13$, 4 Hz, 1H).

Synthesis of azide 300

5 A solution of nitrile alcohol **298** (600 mg, 2.50 mmol) in methylene chloride (14 mL) was cooled to 0°C under argon and treated with triethylamine (0.70 mL, 5.0 mmol) and methanesulfonyl chloride (0.22 mL, 2.8 mmol). The reaction mixture was warmed to 23°C for 0.5 h and subsequently diluted with methylene chloride (50 mL), washed with 1 M hydrochloric acid (15 mL), saturated aqueous sodium bicarbonate (15 mL), and saturated aqueous sodium
10 chloride (15 mL). Drying (Na_2SO_4) and evaporation provided mesylate **299** (0.62 g, 2.0 mmol, 80%) as a white powder. Data for **299**: ^1H NMR (300 MHz, CDCl_3): δ 7.63 (dd, $J = 12$, 2 Hz, 1H), 7.56 (dd, $J = 9$, 7 Hz, 1H), 7.31 (dd, $J = 9$, 2 Hz, 1H), 5.01–4.94 (m, 1H), 4.51 (dd, $J = 12$, 3 Hz, 1H), 4.43 (dd, $J = 12$, 4 Hz, 1H), 4.22–4.15 (m, 1H), 3.96 (dd, $J = 9$, 6 Hz, 1H), 3.45 (dd, $J = 15$, 7 Hz, 1H), 3.06 (s, 3H).

15 A solution of mesylate **299** (0.61 g, 1.9 mmol) in dimethylformamide (15 mL) was treated with sodium azide (0.26 g, 4.0 mmol) and stirred at 75 °C under argon for 1 h. The reaction mixture was cooled to 23°C, diluted with water (100 mL) and extracted with methylene chloride (3×50 mL). The combined organic layer was washed with water (100 mL). The solvent was evaporated and the residue redissolved in ethyl acetate (50 mL) and washed with
20 water (100 mL). Drying (Na_2SO_4) and evaporation provided azide **300** (0.38 g, 1.5 mmol, 79%) as a brown oil. Data for **300**: ^1H NMR (300 MHz, CDCl_3): δ 7.61–7.52 (m, 2H), 7.28 (dd, $J = 9$, 2 Hz, 1H), 4.84–4.76 (m, 1H), 4.08–4.02 (m, 1H), 3.83 (dd, $J = 9$, 6 Hz, 1H), 3.72 (dd, $J = 13$, 4 Hz, 1H), 3.55 (dd, $J = 13$, 4 Hz, 1H).

25 Synthesis of triazole 219

 A solution of alkyne **173** (0.15 g, 0.19 mmol) and azide **300** (0.060 g, 0.21 mmol) in tetrahydrofuran (1.5 mL) was treated with *N,N*-diisopropylethylamine (0.066 mL, 0.38 mmol) and copper (I) iodide (19 mg, 0.10 mmol) and stirred under argon at 23°C for 1 h. The reaction mixture was diluted with saturated aqueous ammonium hydroxide (10 mL) and extracted with
30 dichloromethane (4×30 mL). The combined organic fractions were dried (Na_2SO_4), evaporated, and the residue purified by flash chromatography (SiO_2 , ammonium hydroxide/methanol/

dichloromethane (0.05:1:9) to provide **219** (100 mg, 0.095 mmol, 50%) as a white powder. Data for **219**: ¹HNMR (300 MHz, CDCl₃, partial): δ 7.62–7.55 (m, 3H), 7.24 (dd, *J* = 9, 2 Hz, 1H), 3.34 (s, 3H), 2.32 (s, 3H), 2.24 (s, 3H), 1.02 (d, *J* = 7 Hz, 3H), 0.92–0.80 (m, 6H).

5 Synthesis of oxadiazole **301**

A solution of nitrile **298** (2.00 g, 8.50 mmol) in methanol (42.5 mL) was treated with potassium carbonate (1.18 g, 8.50 mmol) and hydroxylamine hydrochloride (1.18 g, 17.0 mmol) and heated to reflux for 18 h. The reaction mixture was cooled to 23°C, diluted with ethyl acetate (100 mL) and washed with water (4 × 100 mL). Drying (Na₂SO₄) and evaporation afforded a brown powder. A solution of crude this hydroxyamidine (1.00 g, 3.7 mmol) in pyridine (17.5 mL) under argon was cooled to 0°C and treated dropwise with a solution of acetic anhydride (0.70 mL, 7.4 mmol) in pyridine (17.5 mL). The reaction mixture was heated to 120°C for 1 h and then cooled to 23°C. The reaction mixture was then diluted with ethyl acetate (50 mL) and washed with 1 M hydrochloric acid (30 mL), saturated aqueous sodium bicarbonate (30 mL), and saturated aqueous sodium chloride (30 mL) and dried (Na₂SO₄). Flash chromatography (SiO₂, 50–75% ethyl acetate/hexanes) afforded the intermediate acetate-protected oxadiazole (0.28 g, 0.84 mmol, 22%) as a white powder. Data for intermediate oxadiazole: MS (ESI) *m/z* 335.9 (M+H)⁺; ¹HNMR (300 MHz, CDCl₃): δ 8.07–8.02 (m, 1H), 7.62 (dd, *J* = 13, 2 Hz, 1H), 7.39 (dd, *J* = 9, 2 Hz, 1H), 4.97–4.89 (m, 1H), 4.41 (dd, *J* = 12, 4 Hz, 1H), 4.33 (dd, *J* = 12, 5 Hz, 1H), 4.21–4.15 (m, 1H), 3.88 (dd, *J* = 9, 6 Hz, 1H), 2.68 (s, 3H), 2.11 (s, 3H).

A solution of the oxadiazole acetate obtained above (0.25 g, 0.75 mmol) in methanol (0.75 mL) was treated with sodium methoxide (0.005 mg, 0.08 mmol) and stirred at 23°C for 1 h. The reaction mixture was quenched with 1 M hydrochloric acid (0.15 mL) and the solvent was evaporated *in vacuo* to provide oxadiazole **301** (0.21 g, 0.72 mmol, 95%) as a white powder. Data for **301**: ¹HNMR (300 MHz, CDCl₃): δ 8.06–8.00 (m, 1H), 7.63 (dd, *J* = 13, 2 Hz, 1H), 7.39 (dd, *J* = 9, 2 Hz, 1H), 4.81 (m, 1H), 4.07 (m, 3H), 3.78 (dd, *J* = 13, 4 Hz, 1H), 2.68 (s, 1H).

Synthesis of azide **302**

A solution of alcohol **301** (0.18 g, 0.61 mmol) in methylene chloride (3.5 mL) was cooled to 0°C under argon and treated with triethylamine (0.18 mL, 1.2 mmol) and methanesulfonyl

chloride (0.050 mL, 0.68 mmol). The reaction mixture was warmed to 23°C for 0.5 h and diluted with methylene chloride (20 mL), washed with 1 M hydrochloric acid (10 mL), saturated aqueous sodium bicarbonate (10 mL), and saturated aqueous sodium chloride (10 mL). Drying (Na₂SO₄) and evaporation provided the intermediate mesylate (0.19 g, 0.51 mmol, 84%) as a white powder: ¹HNMR (300 MHz, CDCl₃, partial): δ 8.02–7.96 (m, 1H), 7.62–7.45 (m, 1H), 4.94–4.87 (m, 1H), 4.46 (dd, *J* = 12, 4 Hz, 1H), 4.39 (dd, *J* = 12, 4 Hz, 1H), 4.17–4.11 (m, 1H), 3.95 (dd, *J* = 9, 6 Hz, 1H), 3.05 (s, 3H), 2.61 (s, 3H).

A solution of the above mesylate (0.18 g, 0.49 mmol) in dimethylformamide (3.7 mL) was treated with sodium azide (64 mg, 0.98 mmol) and stirred at 75°C under argon for 2 h. The reaction mixture was cooled to 23°C, poured into H₂O (50 mL), and stirred at 0°C. The resulting precipitate was filtered, washed with H₂O, and dried under reduced pressure to provide azide **302** (80 mg, 0.25 mmol, 51%) as a white powder. Data for **302**: ¹HNMR (300 MHz, CDCl₃): δ 8.05 (m, 1H), 7.62 (dd, *J* = 13, 2 Hz, 1H), 7.41–7.39 (m, 1H), 4.88–4.81 (m, 1H), 4.16–4.10 (m, 1H), 3.92 (dd, *J* = 9, 6 Hz, 1H), 3.76 (dd, *J* = 13, 5 Hz, 1H), 3.63 (dd, *J* = 13, 4 Hz, 1H), 2.68 (s, 3H).

Synthesis of triazole **220**

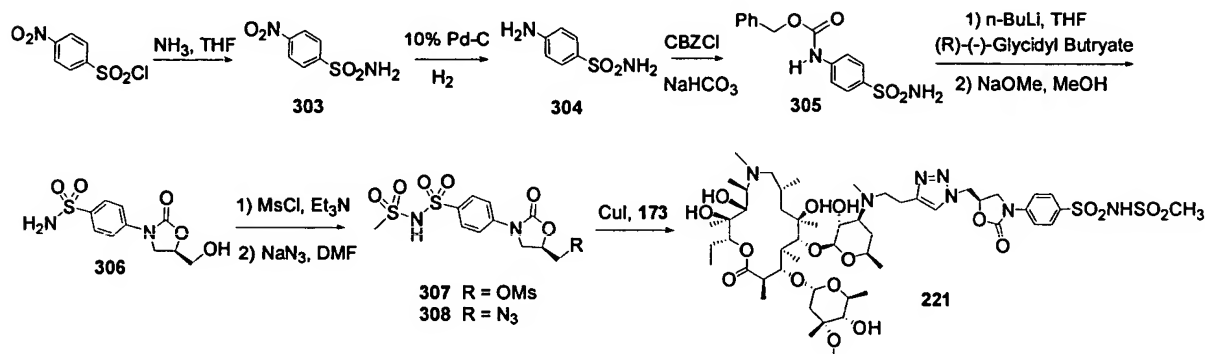
A solution of alkyne **173** (0.13 g, 0.16 mmol) and azide **302** (0.060 g, 0.19 mmol) in tetrahydrofuran (1.2 mL) was treated with *N,N*-diisopropylethylamine (0.044 mL, 0.32 mmol) and copper (I) iodide (15 mg, 0.080 mmol) and stirred under argon at 23°C for 0.5 h. The reaction mixture was diluted with saturated aqueous ammonium hydroxide (10 mL) and extracted with dichloromethane (4 × 30 mL). The combined organic fractions were dried (Na₂SO₄), evaporated, and the residue purified by flash chromatography (SiO₂, ammonium hydroxide/methanol/dichloromethane (0.05:1:9)) to provide **220** (70 mg, 0.063 mmol, 40%) as a white powder. Data for **220**: MS (ESI) *m/z* 1105.5 (M+H)⁺; ¹HNMR (300 MHz, CDCl₃, partial): δ 8.04–7.98 (m, 1H), 7.65 (s, 1H), 7.57–7.53 (m, 1H), 7.27–7.24 (m, 1H), 4.81–4.68 (m, 1H), 4.76–4.73 (m, 1H), 4.43 (d, *J* = 7 Hz, 1H), 3.35 (s, 3H), 0.99–0.81 (m, 6H).

Example 28 – Synthesis of Triazole **221**

Scheme 52 details the synthesis of triazole **221**. *p*-Nitrobenzenesulfonyl chloride was treated with ammonia to provide sulfonamide **303**. The nitro group was reduced to provide aniline **304** which was converted to carbamate **305**. Oxazolidinone formation to yield alcohol

306 was followed by standard manipulations to afford azide **308**. Cycloaddition of **308** with alkyne **173** yielded triazole **221**.

Scheme 52



Synthesis of sulfonamide **303**

4-Nitrobenzenesulfonyl chloride (2.22 g, 10 mmol) was added to a solution of concentrated ammonium hydroxide (3 mL) in THF (5 mL) at 0°C. The reaction was stirred at 0°C for 1 h and then at room temperature for additional 1 h. The THF was removed under vacuum, more water was added, and the precipitate was collected by filtration and dried to afford **303** (1.90 g, 94% yield).

Synthesis of aniline **304**

To a solution of 4-nitrobenzenesulfonamide **303** (1.9 g, 9.4 mmol) in methanol (20 mL) was added 10% Pd-C (0.19 g) and the resulted mixture was stirred at room temperature for 12 h under 1 atm hydrogen atmosphere. The Pd-C was removed by filtration on celite. The filtered solution was evaporated to provide **304** (1.4 g, 87% yield) as a white solid. Data for **304**: ¹HNMR (300 MHz, CDCl₃-CD₃OD): δ 7.63 (d, *J* = 9 Hz, 2H), 6.70 (d, *J* = 9 Hz, 2H).

Synthesis of carbamate **305**

Benzyl chloroformate (1.4 mL, 9.6 mmol) was added dropwise to a solution of aniline **304** (1.38 g, 8.0 mmol), and NaHCO₃ (2.69 g, 21 mmol) in a mixture of THF (5 mL) and water (3 mL) at 0°C. After stirring at same temperature 2 h, the reaction mixture was diluted with ethyl acetate (30 mL). The organic layer was washed with brine (3 x 50 mL), dried (MgSO₄) and

concentrated to provide 2.35 g of white solid **305** in a yield of 96%. Data for **305**: ^1H NMR (300 MHz, CD_3OD): δ 7.80 (d, J = 9 Hz, 2H), 7.61 (d, J = 9 Hz, 2H), 7.43-7.33 (m, 5H), 5.20 (s, 2H).

Synthesis of alcohol **306**

5 To a solution of carbamate **305** (440 mg, 1.44 mmol) in THF (10 mL) was added $n\text{-BuLi}$ (2.0 mL, 2.5 M in hexane, 5.03 mmol) at -78°C and the mixture was stirred for 30 min. (*R*)-(-)-Glycidyl butyrate (0.25 mL, 1.73 mmol) was added, the reaction was stirred at -78°C for 3 h, and then warmed to room temperature and stirred overnight. The reaction was carefully quenched with saturated NH_4Cl and extracted with EtOAc. The organic phase was washed with brine,
10 dried (MgSO_4) and concentrated. The residue was dissolved in 10 mL of methanol and sodium methoxide (0.2 mL, 30% wt/wt in methanol) was added. After stirring at room temperature for 2 h, the mixture was concentrated and purified by chromatography (25:1:0.05/ CH_2Cl_2 :MeOH: $\text{NH}_3\cdot\text{H}_2\text{O}$) to afford 100 mg of desired oxazolidinone **306** in a yield of 26%. Data for **306**: ^1H NMR (300 MHz, CD_3OD): δ 7.90 (d, J = 9 Hz, 2H), 7.78 (d, J = 9 Hz, 2H), 4.77 (m, 1H), 4.18 (t, J = 9 Hz, 1H), 3.99 (dd, J = 6, 9 Hz, 1H), 3.87 (dd, J = 3, 12 Hz, 1H), 3.71 (dd, J = 3, 12 Hz, 1H).
15

Synthesis of azide **308**

To a solution of alcohol **306** (106 mg, 0.39 mmol), Et_3N (129 mg, 1.28 mmol) and 4-dimethylaminopyridine (1 mg) in CH_2Cl_2 (10 mL) and DMF (2 mL) was added methanesulfonyl chloride (150 mg, 1.31 mmol) at 0°C , and the mixture was stirred for 2 h. The reaction mixture was concentrated and purified by chromatography on silica gel (10:1:0.05/ CH_2Cl_2 :MeOH: $\text{NH}_3\cdot\text{H}_2\text{O}$) to afford mesylate **307** (135 mg, 81% yield). Data for **307**: ^1H NMR (300 MHz, CDCl_3): δ 7.85 (d, J = 9 Hz, 2H), 7.54 (d, J = 9 Hz, 2H), 4.96 (m, 1H), 4.50 (dd, J = 3, 12 Hz, 1H), 4.42 (dd, J = 3, 12 Hz, 1H), 4.16 (t, J = 9 Hz, 1H), 3.89 (dd, J = 6, 9 Hz, 1H), 2.90 (s, 3H), 2.80 (s, 3H).
25

A mixture of **307** (135 mg, 0.30 mmol) and sodium azide (101 mg, 1.56 mmol) in DMF (1 mL) was heated at 80°C for 2 h. The reaction mixture was diluted with CH_2Cl_2 (10 mL), filtered, concentrated and purified by flash chromatography to afford crude azide **308** (118 mg),
30 which was of sufficient purity to be used in subsequent reactions. Data for **308**: ^1H NMR (300 MHz, $\text{CDCl}_3\text{-CD}_3\text{OD}$): δ 7.73 (d, J = 8 Hz, 2H), 7.43 (d, J = 8 Hz, 2H), 4.67 (m, 1H), 3.97 (t, J

= 9 Hz, 1H), 3.71(dd, J = 7, 8 Hz, 1H), 3.57 (dd, J = 3, 13 Hz, 1H), 3.41 (dd, J = 4, 13 Hz, 1H), 2.76 (s, 3H).

Synthesis of triazole 221

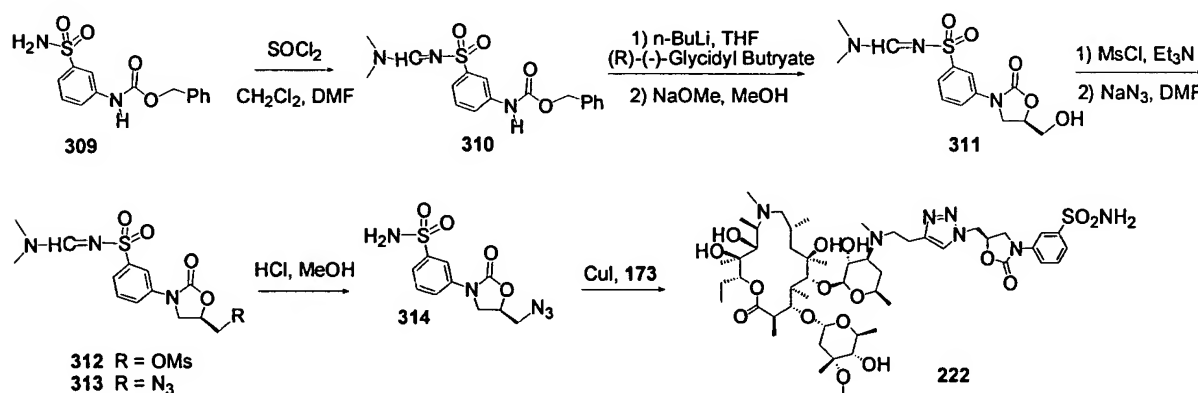
5 A mixture of alkyne **173** (118 mg, 0.15 mmol), azide **308** (118 mg, prepared as above) and copper (I) iodide (28.5 mg, 0.15 mmol) in THF (5 mL) was repeatedly degassed and flushed with argon. i -Pr₂NEt (0.26 mL) was introduced and the mixture was stirred at room temperature for 2 h. The reaction mixture was poured into saturated NH₄Cl (30 mL) and stirred for 15 minutes. The mixture was extracted with CH₂Cl₂, washed with brine, dried over MgSO₄ and
10 concentrated. The crude material was chromatographed on silica gel (10:1:0.05 CH₂Cl₂/MeOH/NH₃·H₂O) to provide triazole **221** (108 mg, 62% yield) as a white foam. Data for **221**: MS (ESI) m/z 1162.3 ($M+H$)⁺; ¹HNMR (300 MHz, CDCl₃-DMSO, partial): δ 7.91 (d, J = 9 Hz, 2H), 7.85 (s, 1H), 7.51 (d, J = 9 Hz, 2H), 3.35 (s, 3H), 3.33 (s, 3H), 3.32 (s, 3H), 0.89 (t, J = 8 Hz, 3H).

15

Example 29 – Synthesis of Triazole 222

Scheme 53 details the synthesis of triazole **222**. Sulfonamide **309** was protected as the sulfonamidine **310** prior to conversion to oxazolidinone alcohol **311**. Alcohol **311** was transformed to azide **314** via functional group interconversion followed by hydrolysis of the
20 amidine protecting group. Cycloaddition of **314** with alkyne **173** provided triazole **222**.

Scheme 53



25 Synthesis of sulfonamidine 310

A solution of sulfonamide **309** (1.10 g, 3.59 mmol, prepared from 3-nitrobenzenesulfonyl chloride by using similar procedures described for the preparation of **305**), thionyl chloride (1.30 mL, 17.97 mmol) and DMF (5 mL) in CH₂Cl₂ (20 mL) was refluxed for 0.5 h. The reaction was cooled with an ice-bath and neutralized with saturated NaHCO₃. The organic phase was separated, washed with brine, dried over MgSO₄ and evaporated to provide **310** as a white solid (1.25 g, 96% yield). Data for **310**: ¹HNMR (300 MHz, CDCl₃): δ 8.12 (s, 1H), 7.81 (t, *J* = 4 Hz, 1H), 7.74 (m, 1H), 7.59 (m, 1H), 7.44-7.35 (m, 6H), 6.98 (br s, 1H), 5.22 (s, 2H), 3.12 (s, 3H), 3.02 (s, 3H).

10 Synthesis of alcohol **311**

To a solution of **310** (724 mg, 2.0 mmol) in THF (16 mL) was added n-BuLi (1.5 mL, 2.5 M in hexane, 3.5 mmol) at -78°C and the mixture was stirred for 30 min. (*R*)-(-)-Glycidyl butyrate (0.35 mL, 2.5 mmol) was added, the reaction was stirred at -78°C for 3 h, and then warmed to room temperature and stirred overnight. The reaction was carefully quenched with saturated NH₄Cl and extracted with EtOAc. The organic phase was washed with brine, dried (MgSO₄) and concentrated. The residue was dissolved in 10 mL of methanol and sodium methoxide (0.2 mL, 30% wt/wt in methanol) was added. After stirring at room temperature for 2 h, the mixture was concentrated and purified by chromatography on silica gel (25:1:0.05/CH₂Cl₂:MeOH:NH₃.H₂O) to afford **311** as a white solid (350 mg, 53% yield). Data for **311**: ¹HNMR (300 MHz, CDCl₃): δ 8.06 (s, 1H), 7.87 (dd, *J* = 2, 8 Hz, 1H), 7.79 (t, *J* = 2 Hz, 1H), 7.57 (m, 1H), 7.39 (t, *J* = 8 Hz, 1H), 4.70 (m, 1H), 3.99 (m, 2H), 3.92 (dd, *J* = 3, 12 Hz, 1H), 3.70 (dd, *J* = 4, 12 Hz, 1H), 3.08 (s, 3H), 2.96 (s, 3H).

Synthesis of azide **314**

To a solution of alcohol **311** (170 mg, 0.52 mmol) and Et₃N (58 mg, 0.57 mmol) in CH₂Cl₂ (10 mL) was added methanesulfonyl chloride (72 mg, 0.62 mmol) at 0°C and the mixture was stirred for 30 min. The CH₂Cl₂ solution was washed with brine, dried (MgSO₄) and concentrated to afford mesylate **312** (200 mg, 95% yield). Data for **312**: ¹HNMR (300 MHz, CDCl₃): δ 8.05 (s, 1H), 7.79 (m, 2H), 7.56 (d, *J* = 8 Hz, 1H), 7.39 (t, *J* = 8 Hz, 1H), 4.90 (m, 1H), 4.45 (dd, *J* = 4, 12 Hz, 1H), 4.37 (dd, *J* = 4, 12 Hz, 1H), 4.14 (t, *J* = 9 Hz, 1H), 3.91 (dd, *J* = 6, 9 Hz, 1H), 3.08 (s, 3H), 3.03 (s, 3H), 2.95 (s, 3H).

A mixture of mesylate **312** (105 mg, 0.26 mmol) and sodium azide (67 mg, 1.04 mmol) in DMF (2 mL) was heated at 80°C for 2 h. The reaction was then diluted with ethyl acetate, washed with brine, dried (MgSO₄) and evaporated to provide azide **313** as a white solid (80 mg, 87% yield). Data for **313**: ¹HNMR (300 MHz, CDCl₃): δ 8.06 (s, 1H), 7.84 (m, 1H), 7.78 (t, *J* = 2 Hz, 1H), 7.56 (d, *J* = 8 Hz, 1H), 7.40 (t, *J* = 8 Hz, 1H), 4.77 (m, 1H), 4.07 (t, *J* = 9 Hz, 1H), 3.84 (dd, *J* = 6, 9 Hz, 1H), 3.67 (dd, *J* = 4, 13 Hz, 1H), 3.53 (dd, *J* = 4, 13 Hz, 1H), 3.08 (s, 3H), 2.95 (s, 3H).

To a solution of azide **313** (80 mg, 0.23 mmol) in methanol (5 mL) was added concentrated HCl (0.5 mL). After refluxing for 4 h, the reaction was cooled with an ice-bath and neutralized with saturated NaHCO₃. The resulting mixture was extracted with CH₂Cl₂, washed with brine, dried over MgSO₄ and evaporated to provide **314** (58 mg, 86% yield). Data for **314**: ¹HNMR (300 MHz, CDCl₃-CD₃OD): δ 7.86 (m, 1H), 7.68 (d, *J* = 8 Hz, 1H), 7.55 (d, *J* = 8 Hz, 1H), 7.39 (t, *J* = 8 Hz, 1H), 4.75 (m, 1H), 4.04 (t, *J* = 9 Hz, 1H), 3.80 (dd, *J* = 6, 9 Hz, 1H), 3.64 (dd, *J* = 4, 13 Hz, 1H), 3.47 (dd, *J* = 4, 13 Hz, 1H).

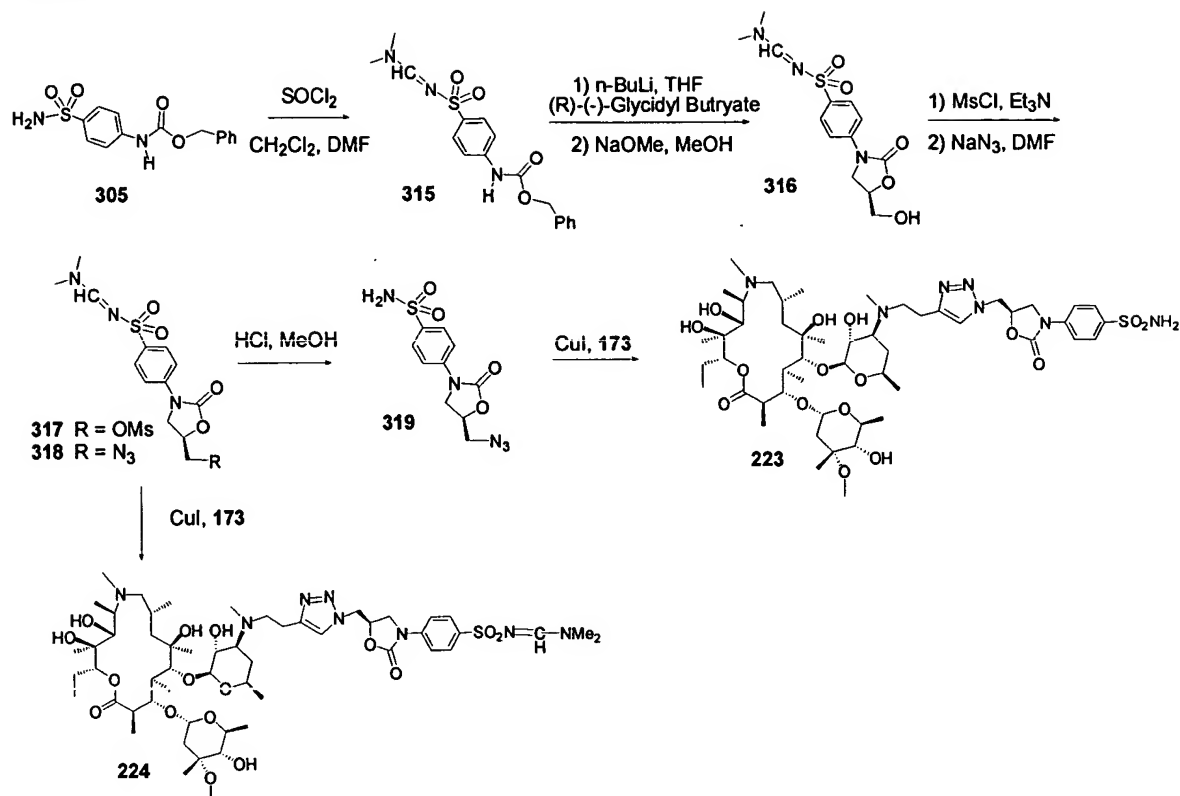
Synthesis of triazole **222**

To a solution of alkyne **173** (79 mg, 0.10 mmol), azide **314** (36 mg, 0.12 mmol) and copper (I) iodide (38 mg, 0.2 mmol) in THF (5 mL) under argon was added *i*-Pr₂NEt (0.18 mL). After stirring at room temperature for 2 h, the reaction mixture was poured into saturated NH₄Cl (30 mL) and stirred for 15 minutes. The mixture was extracted with CH₂Cl₂, washed with brine, dried over MgSO₄ and concentrated. The crude material was chromatographed on silica (10:1 CH₂Cl₂/MeOH) to provide triazole **222** (65 mg, 60% yield) as a white foam. Data for **222**: MS (ESI) *m/z* 1084.4 (M+H)⁺; ¹HNMR (300 MHz, CDCl₃-DMSO, partial): δ 7.76 (s, 1H), 7.71 (d, *J* = 8 Hz, 1H), 7.59 (s, 1H), 7.57 (s, 1H), 7.36 (t, *J* = 8 Hz, 1H), 0.81 (t, *J* = 7 Hz, 3H).

Example 30 – Synthesis of Triazoles **223** and **224**

Scheme 54 details the synthesis of triazoles **223** and **224**. Sulfonamide **305** was protected as sulfonamidine **315** prior to conversion to oxazolidinone alcohol **316**. Transformation of **316** to azide **319** as described previously was followed by cycloaddition of **319** with alkyne **173** to produce triazole **223**. The cycloaddition of intermediate azide **318** with alkyne **173** afforded triazole **224**.

Scheme 54



Synthesis of sulfonamidine **315**

- 5 Sulfonamidine **315** was synthesized using the same procedure described for the preparation of **310**; 0.92 g of **305** afforded 1.02 g of **315** (94% yield). Data for **315**: ^1H NMR (300 MHz, CDCl_3): δ 8.10 (s, 1H), 7.81 (d, $J = 9$ Hz, 2H), 7.47 (d, $J = 9$ Hz, 2H), 7.41-7.34 (m, 5H), 6.89 (br s, 1H), 5.20 (s, 2H), 3.11 (s, 3H), 3.00 (s, 3H).

10 Synthesis of alcohol **316**

Alcohol **316** was synthesized using the same procedure described for the preparation of **311**; 0.97 g of **315** afforded 0.60 g of **316** (69% yield). Data for **316**: ^1H NMR (300 MHz, $\text{CDCl}_3\text{-CD}_3\text{OD}$): δ 8.03 (s, 1H), 7.79 (d, $J = 9$ Hz, 2H), 7.59 (d, $J = 9$ Hz, 2H), 4.68 (m, 1H), 3.98 (m, 2H), 3.84 (dd, $J = 4, 13$ Hz, 1H), 3.64 (dd, $J = 4, 13$ Hz, 1H), 3.08 (s, 3H), 2.95 (s, 3H).

15

Synthesis of azide **318**

Mesylate **317** was synthesized using the same procedure described for the preparation of **312**; 176 mg of **316** afforded 210 mg of **317** (96% yield). Data for **317**: ¹HNMR (300 MHz, CDCl₃): δ 8.06 (s, 1H), 7.83 (d, *J* = 9 Hz, 2H), 7.57 (d, *J* = 9 Hz, 2H), 4.90 (m, 1H), 4.41 (m, 2H), 4.13 (t, *J* = 9 Hz, 1H), 3.94 (dd, *J* = 6, 9 Hz, 1H), 3.10 (s, 3H), 3.06 (s, 3H), 2.95 (s, 3H).

5 Azide **318** was synthesized using the same procedure described for the preparation of **313**; 210 mg of **317** afforded 180 mg of **318** (98% yield). Data for **318**: ¹HNMR (300 MHz, CDCl₃): δ 8.04 (s, 1H), 7.82 (d, *J* = 9 Hz, 2H), 7.60 (d, *J* = 9 Hz, 2H), 4.90 (m, 1H), 4.08 (t, *J* = 9 Hz, 1H), 3.85 (dd, *J* = 6, 9 Hz, 1H), 3.70 (dd, *J* = 4, 13 Hz, 1H), 3.55 (dd, *J* = 4, 13 Hz, 1H), 3.09 (s, 3H), 2.96 (s, 3H).

Synthesis of azide **319**

Azide **319** was synthesized using the same procedure described for the preparation of **314**; 150 mg of **318** afforded 118 mg of **319** (93% yield). Data for **319**: ¹HNMR (300 MHz, CDCl₃-CD₃OD): δ 7.78 (d, *J* = 9 Hz, 2H), 7.56 (d, *J* = 9 Hz, 2H), 4.74 (m, 1H), 4.04 (t, *J* = 9 Hz, 1H), 3.80 (dd, *J* = 6, 9 Hz, 1H), 3.64 (dd, *J* = 4, 13 Hz, 1H), 3.48 (dd, *J* = 4, 13 Hz, 1H).

Synthesis of triazole **223**

20 Triazole **223** was synthesized using the same procedure described for the preparation of **222**; the reaction of alkyne **173** (118 mg, 0.15 mmol) and azide **319** (54 mg, 0.18 mmol) afforded 150 mg of **223** (92% yield). Data for **223**: MS (ESI) *m/z* 1084.4 (M+H)⁺; ¹HNMR (300 MHz, CDCl₃, partial): δ 7.77 (d, *J* = 9 Hz, 2H), 7.55 (s, 1H), 7.45 (d, *J* = 9 Hz, 2H), 3.26 (s, 3H), 0.82 (t, *J* = 8 Hz, 3H).

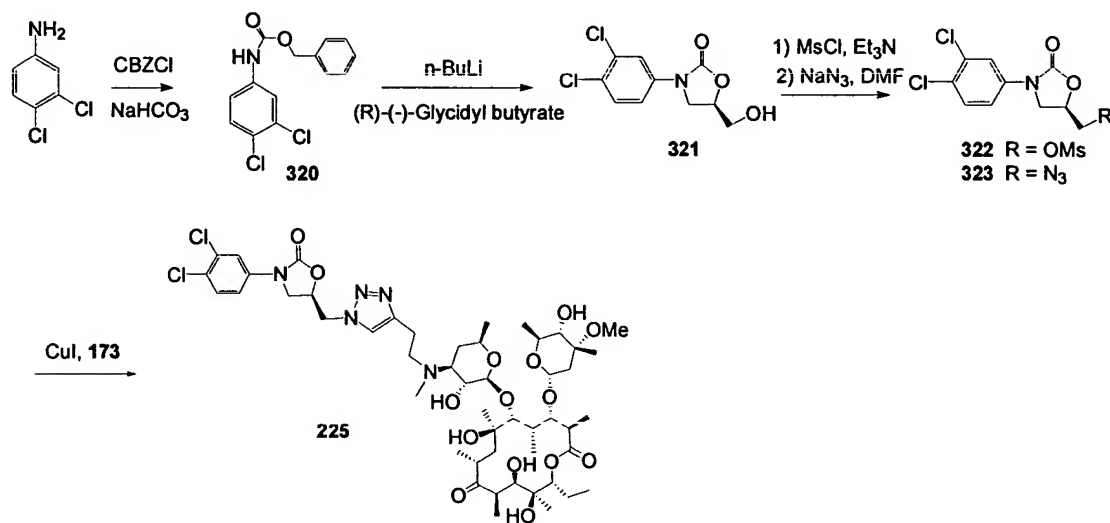
Synthesis of triazole **224**

25 Triazole **224** was synthesized using the same procedure described for the preparation of **222**; the reaction of alkyne **173** (79 mg, 0.10 mmol) and azide **318** (43 mg, 0.12 mmol) afforded 93 mg of **224** (82% yield). Data for **224**: MS (ESI) *m/z* 1139.7 (M+H)⁺; ¹HNMR (300 MHz, CDCl₃, partial): δ 8.04 (s, 1H), 7.78 (d, *J* = 9 Hz, 2H), 7.54 (s, 1H), 7.45 (d, *J* = 9 Hz, 2H), 3.27 (s, 3H), 3.07 (s, 3H), 2.94 (s, 3H), 0.82 (t, *J* = 8 Hz, 3H).

Example 31 – Synthesis of Triazoles 225-227

Scheme 55 details the synthesis of triazole **225**. 3,4-Dichloroaniline was converted to carbamate **320** before being carried further through alcohol **321** to azide **323**. The cycloaddition of **323** with alkyne **173** gave triazole **225**. Triazoles **226** and **227** were synthesized from the requisite anilines using the same sequence as described in Scheme 55.

Scheme 55



10 Synthesis of carbamate **320**

Sodium bicarbonate (2.60 g, 24.7 mmol) was dissolved in water (22 mL) and 3,4-dichloroaniline (2.0 g, 12.34 mmol) was added. The mixture was cooled to 0°C, and benzyl chloroformate (1.76 mL, 12.34 mmol) was added. The mixture was stirred 5 min at 0°C, the cold bath removed, and then stirring was continued at room temperature overnight (~16 hours).

15 The mixture was evaporated, and partitioned with a 1:1 mixture of ethyl acetate and water. The organic layer was washed with water, and then brine. The organic layer was dried with Na₂SO₄, and evaporated to yield **320** (3.60 g, 99% yield) of suitable purity for use in subsequent reactions. Data for **320**: ¹HNMR (300 MHz, CDCl₃): δ 7.18-7.14 (m, 5H), 7.42 (s, 1H), 6.98 (dd, *J* = 11, 3 Hz, 1H), 6.48 (s, 1H), 5.06 (s, 2H).

20

Synthesis of alcohol **321**

Carbamate **320** (3.60g, 12.16 mmol) was dissolved in 10 mL tetrahydrofuran, and the solution cooled to -78°C. *n*-Butyllithium (2.5 M in hexane, 7.6 mL, 12.16 mmol) was added slowly, and the mixture allowed to stir for 45 min at -78°C. *R*-(-)-Glycidyl butyrate (1.75 mL, 12.16 mmol) was added, and the mixture was stirred for 1 h at -78°C. The bath was removed and the reaction allowed to stir overnight at room temperature. The reaction was quenched with 25 mL saturated ammonium chloride solution, and partitioned with ethyl acetate and water. The aqueous layer was extracted thrice with ethyl acetate, and the combined organic layer was washed with brine, dried (Na₂SO₄), and evaporated to yield **321** (2.80 g, 88% yield) of suitable purity for use in subsequent reactions. Data for **321**: ¹HNMR (300 MHz, CDCl₃): δ 7.59 (s, 1H), 7.33 (s, 1H), 4.68 (m, 1H), 3.91 (m, 3H), 3.67 (dd, *J* = 16, 4 Hz, 1H).

Synthesis of azide **323**

Alcohol **321** (2.80 g, 10.68 mmol) was dissolved in 10 mL methylene chloride, and the mixture cooled to 0°C. Triethylamine (3.0 mL, 21.37 mmol) was added, followed by methanesulfonyl chloride (1.15 mL, 15.0 mmol). The mixture was allowed to warm to room temperature and stirred for 1 h. Methylene chloride (20 mL) was added, and the mixture washed twice with 1N HCl, then twice with 10% aqueous sodium carbonate, and then brine. The organic phase was dried (Na₂SO₄), and evaporated to yield mesylate **322** (3.60 g, 99% yield). Data for **322**: ¹HNMR (300 MHz, CDCl₃): δ 7.67 (s, 1H), 7.42 (s, 2H), 4.94 (m, 1H), 4.47 (m, 2H), 4.26 (m, 1H), 4.0 (m, 1H), 3.03 (s, 3H).

A solution of mesylate **322** (3.60 g, 10.58 mmol) in dimethylformamide (10 mL) was treated with sodium azide (2.6 g, 40.21 mmol) and the mixture heated to 80°C for 5 h. The reaction mixture was cooled to room temperature, diluted with ethyl acetate (100 mL), and washed with brine (2 x 50 mL). Drying (Na₂SO₄), and evaporation provided azide **323** (2.53g, 84% yield) as a yellow solid of suitable purity for use in subsequent reactions. Data for **323**: ¹HNMR (300 MHz, CDCl₃): δ 7.61 (s, 1H), 7.30 (s, 2H), 4.75 (m, 1H), 4.01 (m, 1H), 3.75 (m, 1H), 3.66 (dd, *J* = 17, 4 Hz, 1H), 3.51 (dd, *J* = 4, 17 Hz, 1H).

Synthesis of triazole **225**

A solution of alkyne **173** (170 mg, 0.220 mmol) in tetrahydrofuran (10 mL) was treated with azide **323** (100 mg, 0.320 mmol), *N,N*-diisopropylethylamine (0.05 mL, 0.22 mmol) and

copper (I) iodide (0.03 g, 0.160 mmol), and the mixture was stirred under argon at room temperature for 16 h. The reaction mixture was diluted with ethyl acetate (50 mL), and washed with brine (2 x 50 mL). The organic phase was dried and evaporated. The residue was purified by preparative thin layer chromatography using (80% CH₂Cl₂, 20% MeOH, 1 % NH₄OH) to provide triazole **225** (180 mg, 77% yield) as a white solid. Data for **225**: MS (ESI) *m/z* 1075 (M+H)⁺; ¹H-NMR (300 MHz, CDCl₃, partial): δ 7.95 (s, 1H), 7.46 (s, 1H), 7.20 (d, *J* = 8 Hz, 1H), 7.04 (s, 2H), 5.04-4.93 (m, 1H), 4.91 (s, 2H), 4.28 (d, *J* = 6 Hz, 1H), 3.98-3.92 (m, 2H), 3.61 (s, 1H), 3.59-3.48 (m, 1H), 3.34 (s, 1H), 3.19 (s, 1H), 3.06 (m, 1H), 2.94 (m, 1H).

10 Synthesis of triazoles **226** and **227**

These compounds were synthesized from the requisite anilines using the procedures described above for the synthesis of triazole **225**.

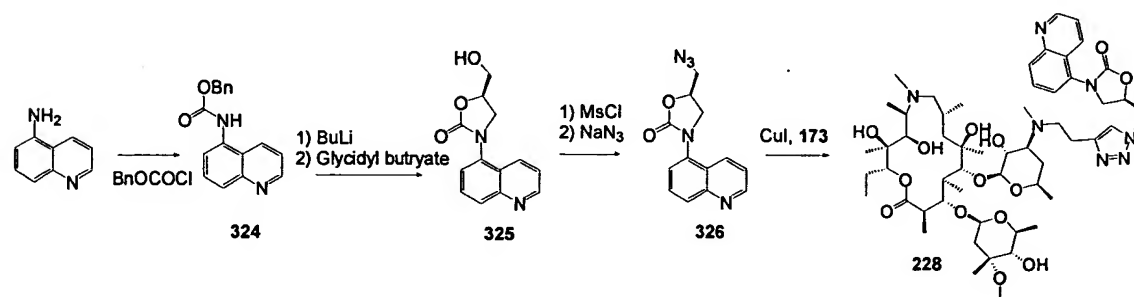
Data for **226**: ¹H-NMR (300 MHz, CDCl₃, partial): δ 8.01 (s, 1H), 7.60 (s, 1H), 7.02 (m, 1H), 6.77 (m, 1H), 4.98-4.68 (m, 1H), 4.37 (s, 2H), 4.13-4.04 (m, 2H), 3.89 (m, 1H), 3.26 (s, 1H), 2.84 (m, 2H), 2.66 (m, 2H).

Data for **227**: ¹H-NMR (300 MHz, CDCl₃, partial): δ 7.50 (s, 1H), 7.00 (s, 1H), 6.82 (d, *J* = 9 Hz, 1H), 6.64 (d, *J* = 9 Hz, 1H), 5.02-4.89 (s, 1H), 4.53 (m, 2H), 4.34 (m, 2H), 3.19 (m, 1H), 2.96 (m, 1H), 2.93 (m, 2H), 2.86 (m, 2H).

20 Example 32 – Synthesis of Triazole **228**

Scheme 56 details the synthesis of triazole **228**. 5-Aminoquinoline was converted to oxazolidinone alcohol **325** via carbamate **324**. The alcohol of **325** was transformed to azide **326**, which was parlayed to triazole **228** via cycloaddition with alkyne **173**.

25 Scheme 56



Synthesis of azide **326**

To a stirred 0°C solution of 5-aminoquinoline (1.0 g, 6.9 mmol) in 2:1 acetone/water (15 mL) was added NaHCO₃ (1.0 g, 13.7 mmol) followed by benzyl chloroformate (1.1 mL, 7.7 mmol). The reaction mixture was allowed to warm to room temperature and stirred for 2h then cooled to 0°C and filtered. The filtrate was washed with water and ether and dried in a vacuum oven at 40°C overnight. The yellow solid (carbamate **324**) thus obtained (1.9 g, 100% yield) was used as-is without further purification.

To a mixture of **324** (1.9 g, 6.9 mmol) in 25 mL THF at -78°C was added 4.3 mL (6.9 mmol) of 1.6M *n*-butyllithium-hexane over 5 minutes. After 30 minutes, 1 mL of (*R*)-glycidyl butyrate was added and the mixture allowed to stir at -78°C for 1 hour and then at room temperature for 16 hr. Saturated ammonium chloride was added (25 mL) followed by ethyl acetate (100 mL). The layers were separated and the aqueous layer extracted with ethyl acetate (3 x 50 mL). The combined organic extracts were dried on MgSO₄, filtered and concentrated to provide 2.3 g of yellow solid which was purified by silica gel chromatography (50 mm x 6" column, eluted with 1:1 hexane/EtOAc to afford alcohol **325** as a yellow solid (450 mg, 27% yield).

To a stirred solution of **325** (300 mg, 1.2 mmol) in DMF (5 mL) was added triethylamine (0.34 mL, 2.4 mmol) followed by methanesulfonyl chloride (95 µL, 1.2 mmol). The mixture was stirred at room temperature and for 2h, and then sodium azide (1 g, 15 mmol) was added and the slurry stirred overnight. The mixture was diluted with water (100 mL) and extracted with ethyl acetate (3 x 50 mL). The combined organic extracts were washed with brine, dried (Na₂SO₄), filtered and concentrated to give 287 mg of azide **326** as an off-white solid which was used without further purification.

Synthesis of triazole **228**

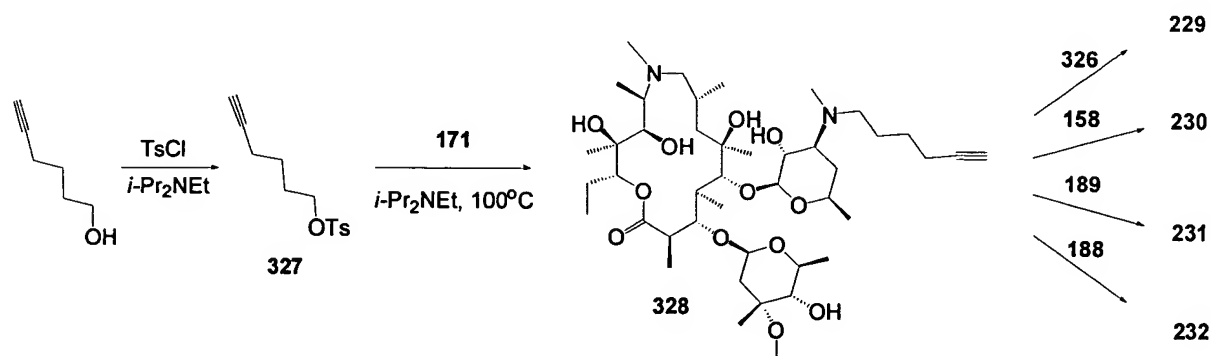
To a stirred solution of alkyne **173** (50 mg, 64 µmol) in THF (250 µL) was added azide **326** (18 mg, 67 µmol) and cuprous iodide (5 mg, 26 µmol). The resulting mixture was degassed by alternately applying vacuum and purging with argon gas. The mixture was stirred under argon at ambient temperature for 16 h. The entire reaction mixture was then placed atop a silica gel flash chromatography column and eluted with 100:3 CH₂Cl₂/ 2N NH₃ in MeOH to afford the

desired triazole adduct **228** as a white solid (50 mg, 74% yield). Data for **228**: MS (ESI) m/z 322.9 ($M+3H$)³⁺, 528.6 ($M+2H$)²⁺, 1056.4 ($M+H$)⁺, 1078.3 ($M+Na$)⁺; ¹HNMR (300 MHz, CDCl₃, partial): δ 9.05 (d, J = 3 Hz, 1H), 8.05 (m, 2H), 7.90 (bs, 1H), 7.71 (dd, J = 8, 3 Hz, 1H), 7.48 (s, 1H), 7.50 (d, J = 7.0 Hz, 1H), 5.18-5.01 (m, 1H), 4.95 (d, J = 5 Hz, 1H), 4.75 (d, J = 4 Hz, 2H), 4.58 (dd, J = 10, 2 Hz, 1H), 4.38 (d, J = 7 Hz, 1H), 4.25 (t, J = 9 Hz, 1H), 4.06 (dd, J = 9, 6 Hz, 1H), 4.08-3.92 (m, 1H), 3.79 (d, J = 7 Hz, 1H), 3.26 (s, 3H), 3.15 (dd, J = 10, 7 Hz, 1H), 2.95 (t, J = 10 Hz, 1H), 2.28 (s, 3H), 2.20 (s, 3H), 0.82 (m, 6H).

Example 33 – Synthesis of Triazoles 229-232

Scheme 57 details the synthesis of targets **229-232**. Hex-5-yn-1-ol was converted to tosylate **327** which served as an alkylating agent for amine **171**. Acetylene **328** was the precursor for cycloaddition reactions with azides **326**, **158**, **189**, and **188** to yield triazoles **229**, **230**, **231**, and **232** respectively.

Scheme 57



Synthesis of tosylate **327**

To a stirred, ice-cold solution of hex-5-yn-1-ol (1.0 g, 10.2 mmol) in ether (20 mL) was added *p*-toluenesulfonyl chloride (2.14 g, 11.2 mmol). Powdered KOH (1.1 g, 20.4 mmol) was then added portion-wise over 5 minutes. The slurry was stirred at 0°C for 3 hours then poured into 100 mL water, and extracted with ether (2 x 50 mL). The combined organic extracts were washed with brine, dried over MgSO₄, filtered, and concentrated to afford **327** as a colorless oil (2.3 g, 89% yield). Data for **327**: ¹HNMR (300 MHz, CDCl₃): δ 7.80 (d, J = 8 Hz, 2H), 7.35 (d, J = 8 Hz, 2H), 4.05 (t, J = 6 Hz, 2H), 2.45 (s, 3H), 2.19 (td, J = 7, 3 Hz, 2H), 1.79 (pent, J = 7 Hz,

2H), 1.55 (pent., $J = 7$ Hz, 2H); ^{13}C NMR (75 MHz, CDCl_3): δ 144.8, 133.0, 129.9, 127.9, 83.4, 69.9, 69.0, 27.7, 24.2, 21.6, 17.7.

Synthesis of alkyne 328

5 A 20 mL vial was charged with tosylate **327** (0.20 g, 0.85 mmol), N-desmethyl azithromycin **171** (0.5 g, 0.68 mmol), and Hunig's base (10 mL), and then purged with argon gas and sealed. The solution was stirred in a 100°C oil bath for 6 h. After cooling to room temperature, the reaction mixture was poured into saturated aqueous NaHCO_3 (50 mL) and extracted with CH_2Cl_2 (3 x 50 mL). The combined organic extracts were washed with brine, 10 dried over K_2CO_3 , filtered, and concentrated to afford 0.8 g of a white solid. Purification by silica gel flash chromatography (25 mm x 6" column eluted with 50:1 CH_2Cl_2 /2N NH_3 in MeOH) gave **328** as a white solid (0.38 g, 68% yield). Data for **328**: MS (ESI) m/z 408.0 ($\text{M}+2\text{H}$) $^{2+}$, 815.3 ($\text{M}+\text{H}$) $^+$.

15 Synthesis of triazole 229

To a stirred solution of alkyne **328** (50 mg, 63 μmol) in THF (250 μL) was added azide **326** (18 mg, 67 μmol) and cuprous iodide (5 mg, 26 μmol). The resulting mixture was degassed by alternately applying vacuum and purging with argon gas. The mixture was stirred under argon at ambient temperature for 16 h. The entire reaction mixture was then placed atop a silica 20 gel flash chromatography column and eluted with 100:3 CH_2Cl_2 / 2N NH_3 in MeOH to afford the desired triazole adduct **229** as a white solid (54 mg, 76% yield). Data for **229**: MS (ESI) m/z 332.2 ($\text{M}+3\text{H}$) $^{3+}$, 542.5 ($\text{M}+2\text{H}$) $^{2+}$, 1070.3 ($\text{M}+\text{H}$) $^+$ 1092.2 ($\text{M}+\text{Na}$) $^+$; ^1H NMR (300 MHz, CDCl_3 , partial): δ 9.10 (d, $J = 3$ Hz, 1H), 8.05 (m, 2H), 8 (bs, 1H), 7.72 (dd, $J = 8, 3$ Hz, 1H), 7.48 (s, 1H), 7.50 (d, $J = 7$ Hz, 1H), 5.20-5.03 (m, 1H), 4.95 (d, $J = 5$ Hz, 1H), 4.75 (d, $J = 4$ Hz, 2H), 25 4.58 (dd, $J = 10, 2$ Hz, 1H), 4.36 (d, $J = 7$ Hz, 1H), 4.23 (t, $J = 9$ Hz, 1H), 4.07 (dd, $J = 9, 6$ Hz, 1H), 4.08-3.94 (m, 1H), 3.79 (d, $J = 7$ Hz, 1H), 3.24 (s, 3H), 3.15 (dd, $J = 10, 7$ Hz, 1H), 2.95 (t, $J = 10$ Hz, 1H), 2.28 (s, 3H), 2.20 (s, 3H), 0.83 (m, 6H).

Synthesis of triazole 230

30 To a stirred solution of **328** (35 mg, 43 μmol) in THF (150 μL) was added Hunig's base (30 μL), azide **158** (28 mg, 86 μmol), and cuprous iodide (4 mg, 21 μmol). The mixture was

degassed by alternately applying vacuum and purging with argon gas. The slurry was stirred under argon at ambient temperature for 4 h. The entire reaction mixture was then placed atop a silica gel flash chromatography column and eluted with 50:1 CH₂Cl₂/ 2N NH₃ in MeOH to afford triazole **230** as a white solid (24 mg, 50% yield). Data for **230**: MS (ESI) *m/z* 568.8

5 (M+2H)²⁺, 1136.4 (M+H)⁺; ¹HNMR (300 MHz, CDCl₃, partial): δ 8.45 (bs, 1H), 7.55 (s, 1H), 7.33 (dd, *J* = 14, 2 Hz, 1H), 6.98 (dd, *J* = 9, 2 Hz, 1H), 6.90 (dd, *J* = 14, 9 Hz, 1H), 5.10-4.95 (m, 2H), 4.80-4.60 (m, 2H), 4.50 (d, *J* = 7 Hz 1H), 3.32 (s, 3H), 2.32 (bs, 3H), 2.22 (bs, 3H), 0.90 (m, 6H).

10 Synthesis of triazole **231**

To a stirred solution of **328** (35 mg, 43 μmol) in THF (150 μL) was added Hunig's base (30 μL), azide **189** (20 mg, 86 μmol) and cuprous iodide (4 mg, 22 μmol). The resulting slurry was degassed by alternately applying vacuum and purging with argon gas. The mixture was stirred under argon at ambient temperature for 4 h. The entire reaction mixture was then placed
15 atop a silica gel flash chromatography column and eluted with 50:1 CH₂Cl₂/ 2N NH₃ in MeOH to afford the triazole adduct **231** as a white solid (31 mg, 70% yield). Data for **231**: MS (ESI) *m/z* 526.4 (M+2H)²⁺, 1073.5 (M+Na)⁺; ¹HNMR (300 MHz, CDCl₃, partial): δ 8.6 (bs, 1H), 7.55 (s, 1H), 7.4-7.2 (m, 2H), 7.08 (dd, *J* = 8, 2 Hz, 1H), 6.78 (td, *J* = 6, 2 Hz, 2H), 5.1-5.0 (m, 2H), 4.8-4.6 (m, 3H), 4.4 (d, *J* = 7 Hz, 1H), 3.95 (dd, *J* = 9, 6 Hz, 1H), 3.31 (s, 3H), 2.32 (bs, 3H),
20 2.25 (s, 3H), 0.82 (m, 6H).

Synthesis of triazole **232**

To a stirred solution of **328** (50 mg, 62 μmol) in THF (150 μL) was added azide **188** (18 mg, 65 μmol) and cuprous iodide (5 mg, 26 μmol). The resulting mixture was degassed by
25 alternately applying vacuum and purging with argon gas. The mixture was stirred under argon at ambient temperature for 16 h. The entire reaction mixture was then placed atop a silica gel flash chromatography column and eluted with 50:1 CH₂Cl₂/2N NH₃ in MeOH to afford the desired triazole adduct **232** as a white solid (54 mg, 81% yield). Data for **232**: MS (ESI) *m/z* 538.4 (M+2H)²⁺, 1075.4 (M+H)⁺; ¹HNMR (300 MHz, CDCl₃, partial): δ 7.87 (dd, *J* = 7, 2 Hz, 2H),
30 7.70 (bs, 1H), 7.45 (dd, *J* = 9, 2 Hz, 2H), 4.90 (d, *J* = 4 Hz, 1H), 4.75-4.60 (m, 2H), 4.58 (d, *J* = 9 Hz, 1H), 4.39 (d, *J* = 7 Hz, 1H), 4.20 (d, *J* = 5 Hz, 1H), 4.18 (t, *J* = 9 Hz, 1H), 4.10-3.90 (m, 1H),

3.92 (dd, $J = 10, 6$ Hz, 1H), 3.32 (s, 3H), 3.15 (dd, $J = 10, 7$ Hz, 1H), 2.95 (t, $J = 10$ Hz, 1H), 2.28 (s, 3H), 2.20 (s, 3H), 0.82 (m, 6H).

Example 34 – Synthesis of Triazoles 233 and 234

5 Synthesis of triazole 233

Compound **180** (50 mg, 49 μ mol) was dissolved in EtOH (1.6 mL), and 1N HCl (aq) was then added (0.4 mL) and the solution stirred at room temperature for 12 h. The reaction mixture was diluted with 10 mL aq. 0.2N HCl and washed with CH₂Cl₂ (3 x 10 mL). The aqueous layer was then adjusted to pH 10 by addition of 2N KOH and extracted with CH₂Cl₂ (2 x 10 mL). The latter two extracts were dried on K₂CO₃, filtered and concentrated to afford **233** as a solid (37 mg, 87% yield). Data for **233**: MS (ESI) m/z 433.4 (M+2H)²⁺, 865.3 (M+H)⁺, 887.3 (M+Na)⁺; ¹HNMR (300 MHz, CDCl₃, partial): δ 7.59 (s, 1H), 7.35-7.20 (m, 2H), 7.05 (dd, $J = 8, 2$ Hz, 1H), 6.78 (td, $J = 8, 2$ Hz, 2H), 4.98 (m, 1H), 4.75-4.60 (m, 3H), 4.35 (d, $J = 7$ Hz, 1H), 4.15-3.98 (m, 2H), 3.88 (dd, $J = 9, 6$ Hz, 1H), 3.7 (dd, $J = 10, 4$ Hz, 1H), 2.31 (bs, 3H), 2.10 (s, 3H), 0.82 (m, 6H).

Synthesis of triazole 234

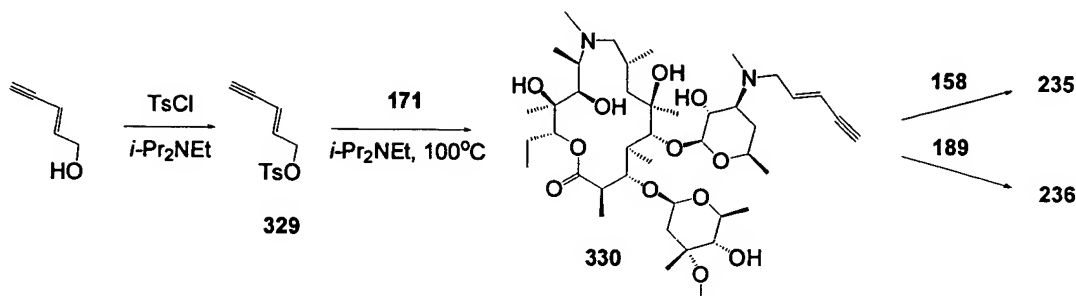
Compound **231** (10 mg, 8.8 μ mol) was dissolved in EtOH (0.8 mL), and 1N HCl (aq) was then added (0.2 mL) and the solution stirred at room temperature for 12 h. The reaction mixture was diluted with 10 mL aq. 0.2N HCl and washed with CH₂Cl₂ (3 x 10 mL). The aqueous layer was then adjusted to pH 10 by addition of 2N KOH and extracted with CH₂Cl₂ (2 x 10 mL). The latter two extracts were dried on K₂CO₃, filtered, and concentrated to afford **234** as a solid (7 mg, 89% yield). Data for **234**: MS (ESI) m/z 447.2 (M+2H)²⁺, 893.5 (M+H)⁺; ¹HNMR (300 MHz, CDCl₃, partial): δ 7.59 (s, 1H) 7.35-7.20 (m, 2H), 7.00 (dd, $J = 8, 2$ Hz, 1H), 6.78 (td, $J = 8, 2$ Hz, 2H), 5.05-4.95 (m, 1H), 4.75-4.60 (m, 3H), 4.40 (d, $J = 7$ Hz 1H), 4.15-3.98 (m, 2H), 3.88 (dd, $J = 9, 6$ Hz, 1H), 3.70 (dd, $J = 10.4, 4.43$ Hz, 1H), 2.31 (bs, 3H), 2.10 (s, 3H), 0.82 (m, 6H).

Example 35 – Synthesis of Triazoles 235 and 236

Scheme 58 illustrates the synthesis of triazoles **235** and **236**. 2-Penten-4-yn-1-ol was converted to tosylate **329** which was used to alkylate amine **171** to yield enyne **330**. The

cycloaddition of alkyne **330** with azide **158** and **189** gave triazole products **235** and **236** respectively.

Scheme 58



Synthesis of tosylate **329**

To a stirred ice-cold solution of 2-penten-4-yn-1-ol (0.821 g, 10 mmol) in ether (25 mL) was added *p*-toluenesulfonyl chloride (2.0 g, 10.5 mmol). Powdered KOH (1.0 g, 17.8 mmol) was then added portionwise over 5 minutes. The slurry was stirred at 0°C for 45 minutes. The reaction mixture was poured into 100 mL water, and extracted with ether (2 x 50 mL). The combined organic extracts were washed with brine, dried over MgSO₄, filtered, and concentrated to afford **329** as a yellow oil (2.1 g, 89% yield). Data for **329**: ¹HNMR (300 MHz, CDCl₃): δ 7.80 (d, *J* = 8 Hz, 2H), 7.35 (d, *J* = 8 Hz, 2H), 6.12 (dt, *J* = 16, 6 Hz, 1H), 5.70 (ddd, *J* = 16, 2, 2 Hz, 1H), 4.60-4.50 (m, 2H), 2.95 (d, *J* = 2, Hz 1H), 2.45 (s, 3H); ¹³C NMR (75 MHz, CDCl₃): δ 145.1, 135.9, 132.9, 130.0, 127.9, 113.9, 80.3, 79.8, 69.0, 21.66.

Synthesis of enyne **330**

A 20 mL vial was charged with tosylate **329** (0.20 g, 0.85 mmol), N-desmethyl azithromycin **171** (0.5g, 0.68 mmol), and Hunig's base (10 mL) then purged with argon gas and sealed. The solution was stirred in a 100°C oil bath for 1h. After cooling to room temperature, the reaction mixture was poured into saturated aqueous NaHCO₃ (50 mL) and extracted with CH₂Cl₂ (3 x 50 mL). The combined organic extracts were washed with brine, dried over K₂CO₃, filtered, and concentrated to afford 0.72 g of a viscous yellow oil. Purification by silica gel flash chromatography (25 mm x 6" column eluted with 50:1 CH₂Cl₂/2N NH₃ in MeOH) gave **330** as a yellow solid (0.48 g, 88% yield). Data for **330**: MS (ESI) *m/z* 400.2 (M+2H)²⁺, 799.3 (M+H)⁺, 821.2 (M+Na)⁺; ¹HNMR (300 MHz, CDCl₃, partial): δ 8.00 (bs, 1H), 6.20 (dt, *J* = 16, 7, Hz,

1H), 5.70-5.60 (m, 1H), 5.00 (d, $J = 4$ Hz, 1H), 4.65 (m, 1H), 4.48 (d, $J = 7$ Hz, 1H), 4.28 (dd, $J = 6, 2$ Hz, 1H), 4.15-3.99 (m, 1H), 3.82 (d, $J = 6$ Hz, 1H), 3.65 (d, $J = 7$ Hz, 1H), 3.60-3.40 (m, 1H), 3.32 (s, 3H), 3.32-3.20 (m, 2H), 2.32 (s, 3H), 2.26 (s, 3H), 0.86 (m, 6H); ^{13}C NMR (75 MHz, CDCl_3): δ 179.3, 144.4, 111.8, 103.8, 96.2, 85.1, 82.6, 79.7, 79.0, 78.5, 77.5, 75.7, 75.3, 74.4, 73.8, 71.9, 71.0, 69.4, 66.5, 65.4, 62.9, 57.0, 50.39, 45.9, 43.4, 42.0, 37.6, 37.5, 35.9, 31.8, 31.2, 28.2, 27.7, 22.8, 22.5, 22.2, 22.0, 19.3, 17.1, 16.3, 12.1, 10.3, 8.6.

Synthesis of triazole 235

To a stirred solution of **330** (20 mg, 25 μmol) in THF (100 μL) was added Hunig's base (20 μL), azide **158** (16 mg, 50 μmol), and cuprous iodide (2.4 mg, 13 μmol). The resulting mixture was degassed by alternately applying vacuum and purging with argon gas. The slurry was stirred under argon at ambient temperature for 4 h. The entire reaction mixture was then placed atop a silica gel flash chromatography column and eluted with 50:1 $\text{CH}_2\text{Cl}_2/2\text{N NH}_3$ in MeOH to afford triazole **235** as a white solid (14 mg, 50% yield). Data for **235**: MS (ESI) m/z 560.8 ($\text{M}+2\text{H}$) $^{2+}$, 1120.5 ($\text{M}+\text{H}$) $^+$; ^1H NMR (300 MHz, CDCl_3 , partial): δ 8.60 (bs, 1H), 7.62 (s, 1H), 7.40-7.20 (m, 1H), 7.00-6.78 (m, 2H), 6.55-6.20 (m, 2H), 5.10-4.90 (m, 2H), 4.50 (d, $J = 10$ Hz 1H), 3.18 (s, 3H), 2.28 (bs, 3H), 2.16 (bs, 3H), 0.90 (m, 6H).

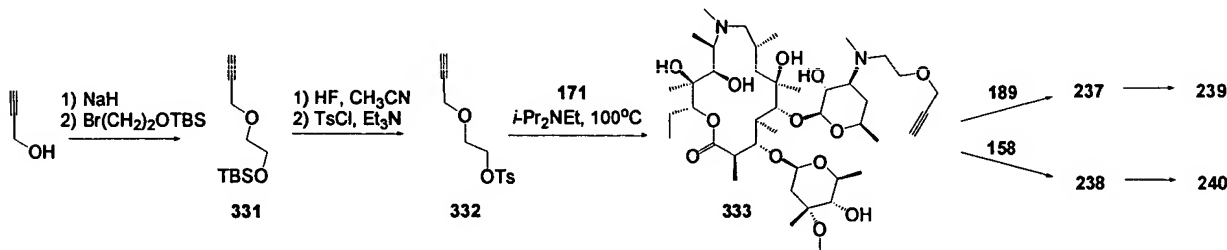
Synthesis of triazole 236

To a stirred solution of **330** (20 mg, 25 μmol) in THF (100 μL) was added Hunig's base (20 μL), azide **189** (16 mg, 50 μmol), and cuprous iodide (2.4 mg, 13 μmol). The resulting mixture was degassed by alternately applying vacuum and purging with argon gas. The slurry was stirred under argon at ambient temperature for 4 h. The entire reaction mixture was then placed atop a silica gel flash chromatography column and eluted with 50:1 $\text{CH}_2\text{Cl}_2/2\text{N NH}_3$ in MeOH to afford the desired triazole adduct **236** as a white solid (18 mg, 70% yield). Data for **236**: MS (ESI) m/z 518.2 ($\text{M}+2\text{H}$) $^{2+}$, 1035.2 ($\text{M}+\text{H}$) $^+$; ^1H NMR (300 MHz, CDCl_3 , partial): δ 8.70 (bs, 1H), 7.65 (s, 1H), 7.40-7.20 (m, 2H), 7.05 (dd, $J = 8, 2$ Hz, 1H), 6.78 (td, $J = 8, 2$ Hz, 2H), 6.60-6.20 (m, 2H), 5.10-4.90 (m, 2H), 4.40 (d, $J = 7$ Hz 1H), 3.86 (dd, $J = 9, 7$ Hz, 1H), 3.21 (s, 3H), 2.22 (bs, 3H), 2.16 (s, 3H), 0.82 (m, 6H).

Example 36 – Synthesis of Triazoles 237-240

Scheme 59 illustrates the synthesis of triazoles 237-240. Propargyl alcohol was alkylated to afford silylether 331 and the silylether subsequently converted to tosylate 332. Alkylation of amine 171 with 332 afforded alkyne 333. Cycloaddition of 333 with azides 189 and 158 yielded triazoles 237 and 238 respectively. Hydrolysis of 237 and 238 provided triazoles 239 and 240.

Scheme 59



Synthesis of silylether 331

To a stirred slurry of sodium hydride (0.28 g, 6.97 mmol) in DMF (30 mL) was added propargyl alcohol (0.41 mL, 6.97 mmol) dropwise over 5 minutes. The mixture was stirred at room temperature for 45 min., then 2-[*t*-butyldimethylsiloxy]-bromoethane (1.8 mL, 8.4 mmol) was added in one portion. After 16 hours the reaction mixture was poured into water (100 mL) and extracted with 1:1 hexane/ether (3 x 50 mL). The combined organic extracts were washed with brine, dried on MgSO₄, filtered and concentrated *in vacuo* to afford 331 as a colorless oil which was used as-is without further purification (1.38 g, 92% yield).

Synthesis of tosylate 332

Silylether 331 (0.86 g, 4 mmol) was dissolved in acetonitrile (20 mL) in a plastic culture tube and cooled to 0°C. Aqueous HF (48% w/w, 1 mL) was then added and the solution stirred at 0°C for 3 hours. The reaction mixture was poured slowly into 100 mL saturated aqueous NaHCO₃ and extracted with ether (3 x 50 mL). The combined organic extracts were washed with brine, dried (K₂CO₃), filtered, and concentrated to afford a colorless oil (0.5g). This oil was dissolved in anhydrous CH₂Cl₂ (5 mL), cooled to 0°C, and then Hunig's base was added (2 mL) followed by tosyl chloride (0.76 g, 4.0 mmol). The reaction mixture was allowed to warm to room temperature and stirred for 6 hours. The solution was diluted with CH₂Cl₂ (50 mL) and washed with saturated aqueous NaHCO₃ and brine. The aqueous washes were back-extracted

with CH₂Cl₂ (50 mL). The combined organic extracts were dried on MgSO₄, filtered, and concentrated to give **332** as a colorless oil (0.81 g, 80% yield). Data for **332**: ¹H NMR (300 MHz, CDCl₃): δ 7.74 (m, 2H), 7.27 (m, 2H), 4.12 (t, *J* = 5 Hz, 2H), 4.05 (d, *J* = 2 Hz, 2H), 3.66 (t, *J* = 5 Hz, 2H), 2.38 (s, 3H), 2.34 (t, *J* = 2 Hz, 1H); ¹³C NMR (75 MHz, CDCl₃): δ 144.8, 133.0, 129.8, 128.0, 78.9, 75.0, 68.8, 67.1, 58.4, 21.6.

Synthesis of alkyne **333**

A 20 mL vial was charged with tosylate **332** (0.20 g, 0.82 mmol), N-desmethyl azithromycin **171** (0.5 g, 0.68 mmol), and Hunig's base (10 mL) and then purged with argon gas and sealed. The solution was stirred in a 100°C oil bath for 6 h. After cooling to room temperature, the reaction mixture was poured into saturated aqueous NaHCO₃ (50 mL) and extracted with CH₂Cl₂ (3 x 50 mL). The combined organic extracts were washed with brine, dried over K₂CO₃, filtered, and concentrated to afford 0.65 g of an off-white solid. Purification by silica gel flash chromatography (25 mm x 6" column eluted with 50:1 CH₂Cl₂/2N NH₃ in MeOH) gave **333** as a white solid (0.22 g, 37% yield). Data for **333**: MS (ESI) *m/z* 409.2 (M+2H)²⁺, 817.0 (M+H)⁺; ¹H NMR (300 MHz, CDCl₃, partial): δ 7.50 (bs, 1H), 4.87 (d, *J* = 4 Hz, 1H), 4.55 (dd, *J* = 10, 2 Hz, 1H), 4.35 (d, *J* = 7 Hz, 1H), 4.20 (dd, *J* = 7, 2 Hz, 1H), 4.06 (d, *J* = 2 Hz, 2H), 4.05-3.90 (m, 1H), 3.57 (d, *J* = 7 Hz, 1H), 3.51 (t, *J* = 6 Hz, 1H), 3.38 (d, *J* = 6 Hz, 1H), 3.24 (s, 3H), 3.15 (dd, *J* = 10, 7 Hz, 1H), 2.93 (t, *J* = 10 Hz, 1H), 2.24 (s, 3H), 2.23 (s, 3H), 0.86 (m, 6H); ¹³C NMR (75 MHz): δ 177.8, 106.84, 95.05, 82.3, 79.3, 76.0, 74.3, 73.1, 70.6, 69.9, 69.5, 65.8, 62.35, 60.34, 52.1, 44.6, 41.9, 37.3, 36.5, 36.1, 29.6, 26.7, 25.8, 21.2, 20.8, 18.6, 16.1, 15.9, 14.2, 10.9, 7.8.

Synthesis of triazole **237**

To a stirred solution of **333** (50 mg, 61 μmol) in THF (150 μL) was added Hunig's base (30 μL), azide **189** (20 mg, 86 μmol), and cuprous iodide (6 mg, 33 μmol). The resulting mixture was degassed by alternately applying vacuum and purging with argon gas. The slurry was stirred under argon at ambient temperature for 4 h. The entire reaction mixture was then placed atop a silica gel flash chromatography column and eluted with 50:1 CH₂Cl₂/2N NH₃ in MeOH to afford the desired triazole adduct **237** as a white solid (31 mg, 70% yield). Data for **237**: MS (ESI) *m/z* 527.4 (M+2H)²⁺, 1075.4 (M+H)⁺; ¹H NMR (300 MHz, CDCl₃, partial): δ

8.10 (bs, 1H), 7.72 (s, 1H), 7.40-7.20 (m, 2H), 7.05 (dd, $J = 8, 2$ Hz, 1H), 6.78 (td, $J = 6, 2$ Hz, 2H), 5.10-4.90 (m, 2H), 4.80-4.60 (m, 4H), 4.40 (d, $J = 7$ Hz, 1H), 4.22 (d, $J = 4$ Hz, 1H), 4.09 (t, $J = 9$ Hz, 1H), 4.10-3.95 (m, 1H), 3.89 (dd, $J = 9, 6$ Hz, 1H), 3.34 (s, 3H), 3.16 (dd, $J = 10, 8$ Hz, 1H), 2.32 (s, 3H), 2.30 (s, 3H), 0.90 (m, 6H).

5

Synthesis of triazole 238

To a stirred solution of **333** (35 mg, 43 μ mol) in THF (150 μ L) was added Hunig's base (30 μ L), azide **158** (28 mg, 86 μ mol), and cuprous iodide (4 mg, 21 μ mol). The mixture was degassed by alternately applying vacuum and purging with argon gas. The mixture was stirred under argon at ambient temperature for 4 h. The entire reaction mixture was then placed atop a silica gel flash chromatography column and eluted with 50:1 $\text{CH}_2\text{Cl}_2/2\text{N NH}_3$ in MeOH to afford the desired triazole adduct as a white solid (24 mg, 50% yield). Data for **238**: MS (ESI) m/z 569.9 ($\text{M}+2\text{H}$) $^{2+}$, 1160.4 ($\text{M}+\text{Na}$) $^+$; ^1H NMR (300 MHz, CDCl_3 , partial): δ 8.05 (bs, 1H), 7.80 (s, 1H), 7.33 (dd, $J = 14, 2$ Hz, 1H), 7.05 (dd, $J = 9, 2$ Hz, 1H), 6.88 (t, $J = 9$ Hz, 1H), 5.18-5.00 (m, 2H), 4.80-4.60 (m, 4H), 4.50 (d, $J = 7$ Hz, 1H), 4.13 (t, $J = 9$ Hz, 1H), 3.92 (dd, $J = 9, 6$ Hz, 1H), 3.34 (s, 3H), 2.32 (s, 3H), 2.30 (s, 3H), 0.90 (m, 6H).

15

Synthesis of triazole 239

Compound **237** (10 mg, 9.8 μ mol) was dissolved in EtOH (0.8 mL) and 1N HCl (aq) was then added (0.2 mL) and the solution stirred at room temperature for 16 h. The reaction mixture was diluted with 10 mL aq. 0.2N HCl and washed with CH_2Cl_2 (3 x 10 mL). The aqueous layer was then adjusted to pH 10 by addition of 2N KOH and extracted with CH_2Cl_2 (2 x 10 mL). The latter two extracts were dried on K_2CO_3 , filtered and concentrated to afford triazole **239** as a solid (7 mg, 80% yield). Data for **239**: MS (ESI) m/z 448.3 ($\text{M}+2\text{H}$) $^{2+}$, 895.3 ($\text{M}+\text{H}$) $^+$.

25

Synthesis of triazole 240

Compound **238** (10 mg, 8.7 μ mol) was dissolved in EtOH (1.6 mL) and 1N HCl (aq) was then added (0.4 mL) and the solution stirred at room temperature for 12 h. The reaction mixture was diluted with 10 mL aq. 0.2N HCl and washed with CH_2Cl_2 (3 x 10 mL). The aqueous layer was then adjusted to pH 10 by addition of 2N KOH and extracted with CH_2Cl_2 (2 x 10 mL). The latter two extracts were dried on K_2CO_3 , filtered and concentrated to afford triazole **240** as a

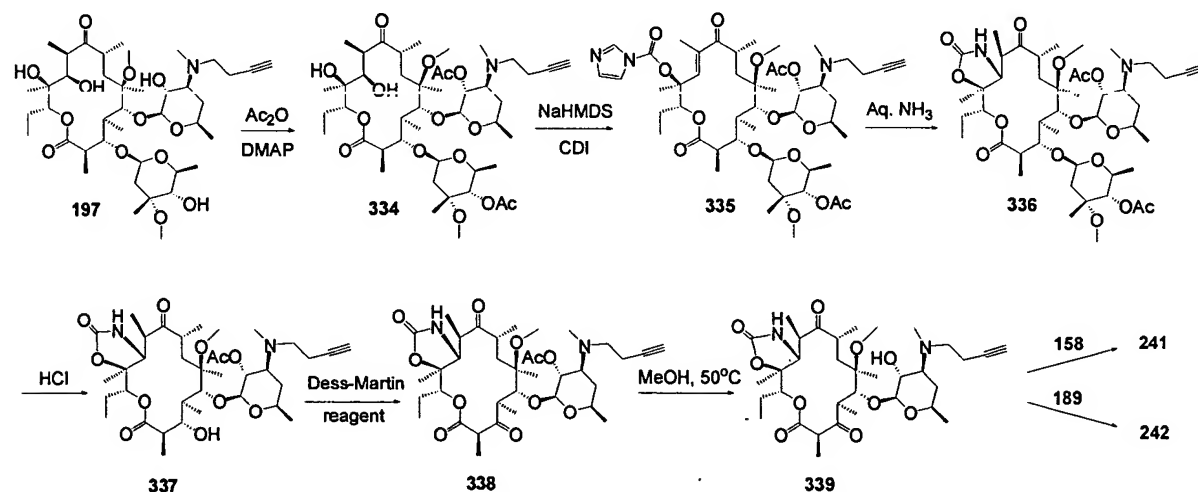
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solid (6 mg, 87% yield). Data for **240**: MS (ESI) m/z 434.4 ($M+2H$)²⁺, 867.2 ($M+H$)⁺, 889.3 ($M+Na$)⁺.

Example 37 – Synthesis of Ketolides 237-240

5 Scheme 60 depicts the synthesis of triazoles **241** and **242**. Alkyne **197** was protected as diacetate **334**, and then **334** was treated with sodium hexamethyldisilylazide and carbonyldiimidazole to provide imidazole carbamate **335**. Michael addition of ammonia to **335** was followed by closure of the amine group onto the imidazole carbamate to afford carbamate **336**. Selective hydrolysis of **336** afforded alcohol **337** which was subsequently oxidized with the Dess-Martin periodinane to yield ketolide **338**. Deprotection of **338** gave alkyne **339**, which was treated with azides **158** and **189** to provide triazoles **241** and **242** respectively.

Scheme 60



15 Synthesis of diacetate **334**

Alkyne **197** (1.50 g, 1.90 mmol) was dissolved in 5 mL methylene chloride and the mixture cooled to $0^\circ C$. Dimethylaminopyridine (47 mg, 0.38 mmol) and triethylamine (0.8 mL, 5.7 mmol) were added, followed by acetic anhydride (0.54 mL, 5.7 mmol). The mixture was allowed to warm to room temperature and stirred for 1.5 h. Methylene chloride (50 mL) was added and the mixture washed with sat. aqueous $NaHCO_3$, and then brine. The organic phase was dried (K_2CO_3) and evaporated to afford 1.9 g of a white solid. The crude solid was purified by silica gel flash chromatography (25 mm x 6" column eluted with 40:1 $CH_2Cl_2/2N NH_3$ in

MeOH) to afford **334** as a white solid (1.4 g, 86% yield). Data for **334**: MS (ESI) m/z 870.2 (M+H)⁺, 892.3 (M+Na)⁺.

Synthesis of imidazole carbamate **335**

A solution of **334** (0.8 g, 0.92 mmol) in 5.0 mL THF was cooled to -40°C, NaHMDS (1.2 mL of a 1.0 M THF soln.) was added dropwise to the stirred solution over 5 min., and the mixture was stirred at -40°C for 40 min. A solution of carbonyldiimidazole (0.60 g, 3.7 mmol) in 8 mL of a 5:3 mixture of THF and DMF was then added over a period of 30 minutes by syringe-pump. Ten minutes after the addition was complete the cold bath was removed and the reaction mixture was allowed to warm to room temperature. After 16 h the reaction mixture was diluted with EtOAc (20 mL) and the washed with sat. aqueous NaHCO₃ and brine. The organic phase was dried (Na₂SO₄), filtered, and evaporated to afford **335** as an off-white solid which was used without further purification (0.92 g, 100% yield). Data for **335**: MS (ESI) m/z 968.4 (M+Na)⁺.

Synthesis of carbamate **336**

A solution of **335** (0.94 g, 0.92 mmol) in acetonitrile (10 mL) was treated with 15% aqueous ammonia (2 mL) and the mixture stirred at room temperature for 40 hours. The reaction mixture was diluted with EtOAc (50 mL), and washed with sat. aqueous NaHCO₃ and brine, the aqueous washes were back-extracted twice with 50 mL portions of EtOAc. The combined organic extracts were dried (Na₂SO₄) and evaporated to afford 1.3 g of an off-white solid. Purification by silica gel flash chromatography (25mm x 6" column eluted with 1:3 acetone/hexanes) gave 260 mg of **336** (31% yield) along with 100 mg of its C-10 epimer and 450 mg of a mixture of the two. Data for **336**: MS (ESI) m/z 895.2 (M+H)⁺, 917.3 (M+Na)⁺.

Synthesis of alcohol **337**

A solution of **336** (209 mg, 0.221 mmol) in 0.1 N aqueous HCl (5 mL) was stirred at room temperature for 8 h. The reaction mixture was neutralized with saturated aqueous NaHCO₃ (50 mL) and extracted with methylene chloride (3 x 25 mL). The combined organic extracts were washed with brine, dried (K₂CO₃), filtered, and evaporated to give 190 mg of a white solid. The crude product was chromatographed on silica gel using a 3:1 hexane/acetone as

the eluant to provide **337** (145 mg, 94% yield) as a white solid. Data for **337**: MS (ESI) m/z 695.2 (M+H)⁺, 717.1 (M+Na)⁺.

Synthesis of ketolide **338**

To a stirred solution of **337** (80 mg, 0.115 mmol) in methylene chloride at 0°C was added Dess-Martin periodinane (59 mg, 0.138 mmol). The reaction mixture was stirred at ambient temperature for 12 hours then placed directly on a silica gel chromatography column and eluted with 3:1 hexane/acetone to afford ketolide **338** (62 mg, 78% yield) as a white solid. Data for **338**: MS (ESI) m/z 693.1 (M+H)⁺, 715.3 (M+Na)⁺.

Synthesis of alkyne **339**

A methanol solution of **338** (62 mg, 0.090 mmol) was stirred at 50°C for 16 h. The reaction mixture was concentrated *in vacuo* to give **339** as a white solid (55 mg, 94% yield) which was used without further purification. Data for **339**: MS (ESI) m/z 651.2 (M+H)⁺, 673.1 (M+Na)⁺.

Synthesis of triazole **241**

To a stirred solution of **339** (20 mg, 31 μmol) in THF (310 μL) was added Hunig's base (26 μL), azide **158** (14.8 mg, 46 μmol), and cuprous iodide (5.8 mg, 31 μmol). The resulting mixture was stirred at ambient temperature for 4 h. The entire reaction mixture was then placed atop a silica gel flash chromatography column and eluted with 50:1 CH₂Cl₂/2N NH₃ in MeOH to afford the desired triazole adduct **241** as a white solid (26 mg, 86% yield). Data for **241**: MS (ESI) m/z 972.3 (M+H)⁺, 994.3 (M+Na)⁺; ¹HNMR (300 MHz, CDCl₃, partial): δ 7.60 (s, 1H), 7.41 (dd, J = 14, 2 Hz, 1H), 7.00-6.60 (m, 2H), 6.75 (bs, 1H), 5.72 (dd, J = 10, 3 Hz 1H), 5.01-4.90 (m, 1H), 4.75-4.52 (m, 3H), 4.33-4.05 (m, 3H), 2.18 (s, 3H), 0.90 (t, J = 7 Hz, 3H).

Synthesis of triazole **242**

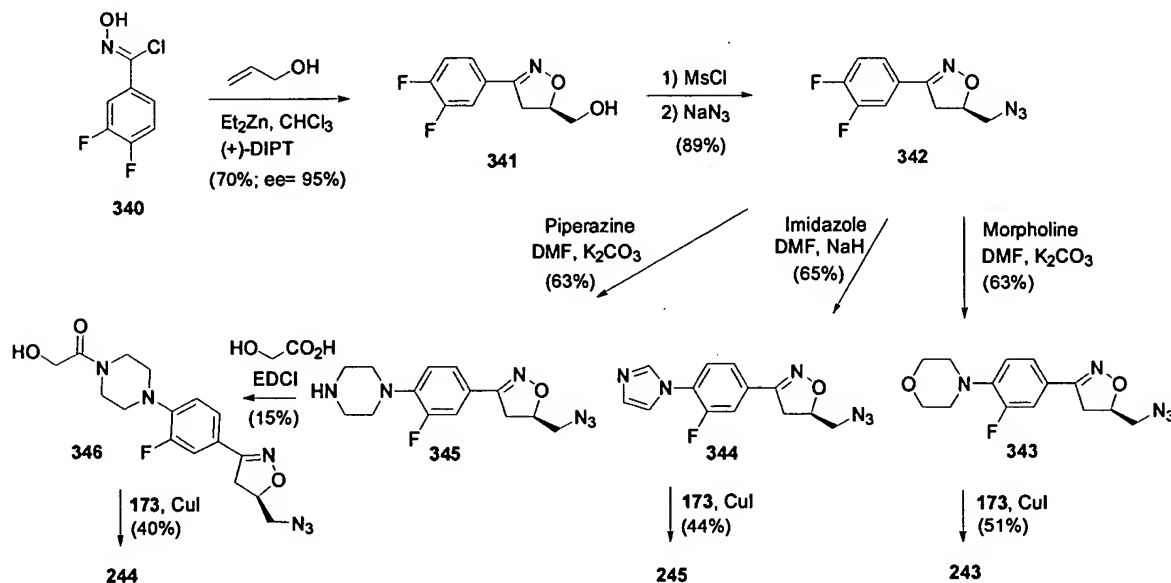
To a stirred solution of **339** (18 mg, 28 μmol) in THF (310 μL) was added Hunig's base (24 μL), azide **189** (10 mg, 42 μmol) and cuprous iodide (5.3 mg, 28 μmol). The resulting mixture was stirred at ambient temperature for 4 h. The entire reaction mixture was then placed atop a silica gel flash chromatography column and eluted with 50:1 CH₂Cl₂/2N NH₃ in MeOH to

afford the desired triazole adduct **242** as a white solid (21mg, 85% yield). Data for **242**: MS (ESI) m/z 887.3 (M+H)⁺, 909.3 (M+Na)⁺; ¹HNMR (300 MHz, CDCl₃, partial): δ 7.65 (s, 1H), 7.55-7.30 (m, 2H), 7.10 (dd, J = 8, 2 Hz, 1H), 6.82-6.70 (m, 1H), 6.75 (bs, 1H), 5.70 (dd, J = 10, 3 Hz 1H), 5.18-4.99 (m, 1H), 4.80-4.52 (m, 3H), 4.33-4.05 (m, 3H), 2.20 (bs, 3H), 0.90 (t, J = 7 Hz, 3H).

Example 38 – Synthesis of Isoxazolines 243-245

Scheme 61 depicts the synthesis of isoxazolines **243-245**. Known hydroxyiminoyl chloride **340** (*J. Med. Chem.* **2003**, *46*, 284) was converted to isoxazoline alcohol **341**. The alcohol group of **341** was transformed to the azide **342**, an intermediate used in subsequent aromatic substitution chemistry with nucleophiles to produce azides **343**, **344** and **345**. Azide **345** was acylated to provide azide **346**. The cycloaddition of azides **343**, **344**, and **346** with alkyne **173** yielded target isoxazolines **243**, **245**, and **244** respectively.

Scheme 61



Synthesis of alcohol 341

To a solution of allyl alcohol (15.6 mL, 0.23 mol) in 600 mL chloroform was added a 1M solution of diethyl zinc in hexanes (276 mL, 0.276 mol) between -10°C to 0°C. After stirring for 10 min, (+)-diisopropyl L-tartrate (9.68 mL, 45.9 mmol) was added and the solution was stirred at 0°C for 1 h. Dioxane (24 mL, 0.282 mol) was added followed by hydroxyiminoyl chloride

340 (40 g, 0.209 mol) and the solution was stirred at -5°C to 0°C for 1½ h, then poured into 1M citric acid/ice (400mL) and extracted with dichloromethane (2x 200 mL). The combined organic extract was washed with water (100 mL), brine (100 mL), dried (Na₂SO₄) and evaporated to a volume of 50 mL. 1-Chlorobutane (250 mL) was added and again the solution evaporated to a volume of 50 mL. The beige suspension was filtered, washed with 1-chlorobutane (2x10 mL) and dried to afford 14.5 g of alcohol **341**. The remaining supernatant was evaporated and purified by flash-chromatography (eluant: hexanes-ethyl acetate 2:1) yielding an additional 22.0 g of alcohol **341**. The combined portions of alcohol **341** were recrystallized from 120 mL 1-chlorobutane-hexanes 4:1, yielding pure alcohol **341** (31.1g, 70% yield, ee: 95% as determined by Mosher ester). Data for **341**: ¹HNMR (300 MHz, CDCl₃): δ 7.55-7.45 (m, 1H), 7.39-7.12 (m, 2H), 4.95-4.83 (m, 1H), 3.91 (dd, *J* = 1, 2 Hz, 1H), 3.69 ((dd, *J* = 1, 2 Hz, 1H), 3.40-3.21 (m, 2H), 2.20 (br s, 1H).

Synthesis of azide **342**

To a solution of **341** (3.0 g, 14.1 mmol) in 60 mL dichloromethane was added Et₃N (3.53 mL, 25.2 mmol) followed by MsCl (1.31 mL, 16.9 mmol) at 0°C. The mixture was stirred at 0°C for 30 min, then poured into 30 mL water/ice and extracted with dichloromethane (2x 50 mL). The combined organic extract was washed with water (2x 30 mL), brine (30 mL), dried (Na₂SO₄) and evaporated. The residue was dissolved in 50 mL DMF, and NaN₃ (1.83 g., 28.1 mmol) was added and the mixture stirred at 80°C for 2 h. The mixture was poured into 30 mL water/ice and extracted with ethyl acetate (2x 50 mL). The combined organic extract was washed with water (2x 30 mL), brine (30 mL), dried (Na₂SO₄) and evaporated. The residual oil was crystallized with 20 mL 1-chlorobutane-hexanes 2:1, yielding azide **342** (3.0 g, 89%). Data for **342**: ¹HNMR (300 MHz, CDCl₃): δ 7.50-7.41 (m, 1H), 7.35-7.05 (m, 2H), 4.92-4.81 (m, 1H), 3.51-3.05 (m, 4H).

Synthesis of azide **343**

A mixture of **342** (400 mg, 1.68 mmol) and K₂CO₃ (302 mg, 2.18 mmol) in 6 mL morpholine was stirred at 120°C for 48 h, then poured into 20 mL water/ice and extracted with ethyl acetate (2x 10 mL). The combined organic extract was washed with water (2x 10 mL), brine (10 mL), dried (Na₂SO₄) and evaporated. The residue was purified by flash-

chromatography (eluant: hexanes-ethyl acetate 2:1) yielding azide **343** (320 mg, 63%). Data for **343**: MS (ESI) m/z 306 ($M+H$)⁺; ¹HNMR (300 MHz, CDCl₃): δ 7.38-7.23 (m, 2H), 6.80-6.78 (m, 1H), 4.90-4.75 (m, 1H), 3.83-3.75 (m, 4H), 3.48-3.25 (m, 4H), 3.18-3.02 (m, 4H).

5 Synthesis of azide **344**

To a solution of imidazole (214 mg, 3.15 mmol) in 5 mL DMF was added NaH (60% dispersion in paraffin oil, 100 mg, 2.52 mmol) at 0°C. After stirring the mixture for 30 min, the azide **342** (0.5 g, 2.1 mmol) was added. The mixture was stirred at room temperature overnight and then 60°C for 2 h, and then poured into 40 mL water/ice and extracted with ethyl acetate (3x 20 mL). The combined organic extract was washed with water (3x 20 mL), brine (10 mL), dried (Na₂SO₄) and evaporated. The residue was purified by flash-chromatography (eluant: ethyl acetate followed by ethyl acetate-MeOH 20:1) yielding azide **344** (390 mg, 65%). Data for **344**: ¹HNMR (300 MHz, CDCl₃): δ 7.92 (s, 1H), 7.72-7.45 (m, 3H), 7.39-7.23 (m, 2H), 5.10-4.96 (m, 1H), 3.69-3.41 (m, 3H), 3.31-3.20 (m, 1H).

Synthesis of azide **345**

A mixture of azide **342** (1.0 g, 4.2 mmol), K₂CO₃ (755 mg, 5.5 mmol) and piperazine (15 g, 175 mmol) was dissolved in 9 mL DMF. The mixture was stirred at 120°C for 3 h, then poured into 50 mL water/ice and extracted with ethyl acetate-isopropanol 95:5 (3x 30 mL). The combined organic extract was washed with water (3x 20 mL), brine (10 mL), dried (Na₂SO₄) and evaporated. The residue was purified by flash-chromatography (eluant: ethyl acetate-MeOH 3:1) yielding azide **345** (793 mg, 63%). Data for **345**: ¹HNMR (300 MHz, CDCl₃): δ 7.52-7.39 (m, 2H), 7.08-6.95 (m, 1H), 5.05-4.92 (m, 1H), 3.63-3.41 (m, 3H), 3.33-3.10 (m, 9H), 1.85 (br s, 1H).

Synthesis of azide **346**

To a solution of azide **345** (300 mg, 0.99 mmol) in 6 mL dichloromethane-DMF 2:1 was added glycolic acid (97.8 mg, 1.29 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI) (284 mg, 1.48 mmol) and diisopropyl ethylamine (0.344 mL, 1.98 mmol) at 0°C. The solution was stirred at room temperature over the weekend and then poured into 20 mL 5% aqueous Na₂CO₃/ice and extracted with ethyl acetate (2x 15 mL). The combined organic

extract was washed with water (2x 10 mL), 10 mL 1M aqueous HCl, water (2x 10 mL), brine (10 mL), dried (Na₂SO₄) and evaporated. The residue was purified by flash-chromatography (eluant: ethyl acetate) yielding azide **346** (51 mg, 15%). Data for **346**: ¹HNMR (300 MHz, CDCl₃): δ 7.39-7.25 (m, 2H), 6.91-6.80 (m, 1H), 4.91-4.79 (m, 1H), 4.15 (s, 2H), 3.83-3.75 (m, 2H), 3.50-3.26 (m, 5H), 3.18-3.04 (m, 5H).

Synthesis of isoxazoline **243**

To a solution of alkyne **173** (100 mg, 0.127 mmol) in 4 mL acetonitrile was added azide **343** (39 mg, 0.127 mmol), 2,6-lutidine (0.0163 mL, 0.139 mmol) and CuI (24mg, 0.127 mmol). The mixture was stirred overnight at room temperature, then poured into 10 mL 5% aqueous NH₃/ice and extracted with ethyl acetate (3x 20 mL). The combined organic extract was washed with water (2x 10 mL), brine (10 mL), dried (Na₂SO₄) and evaporated. The residue was purified by flash-chromatography (eluant: ethyl acetate-MeOH 5:1) yielding **243** (71 mg, 51%). Data for **243**: MS (ESI) *m/z* 1092 (M+H)⁺; ¹HNMR (300 MHz, CDCl₃, partial): δ 8.31-8.21 (br s, 1H), 7.51 (s, 1H), 7.31-7.12 (m, 2H), 6.81 (t, *J* = 1 Hz, 1H), 5.05-4.90 (s, 1H), 4.65-3.90 (m, 5H), 3.81-3.74 (m, 2H).

Synthesis of isoxazoline **244**

To a solution of alkyne **173** (100 mg, 0.127 mmol) in 4 mL acetonitrile was added azide **346** (46 mg, 0.127 mmol), 2,6-lutidine (0.0163 mL, 0.139 mmol) and CuI (14.5 mg, 0.076 mmol). The mixture was stirred overnight at room temperature, then poured into 10 mL 5% aqueous NH₃/ice and extracted with ethyl acetate (3x 20 mL). The combined organic extract was washed with water (2x 10 mL), brine (10 mL), dried (Na₂SO₄) and evaporated. The residue was purified by flash-chromatography (eluant: ethyl acetate-MeOH 5:1) yielding **244** (58 mg, 40%). Data for **244**: MS (ESI) *m/z* 1049 (M+H)⁺; ¹HNMR (300 MHz, CDCl₃, partial): δ 7.54 (s, 1H), 7.31-7.13 (m, 2H), 7.85-7.72 (m, 1H), 5.10-4.95 (m, 1H).

Synthesis of isoxazoline **245**

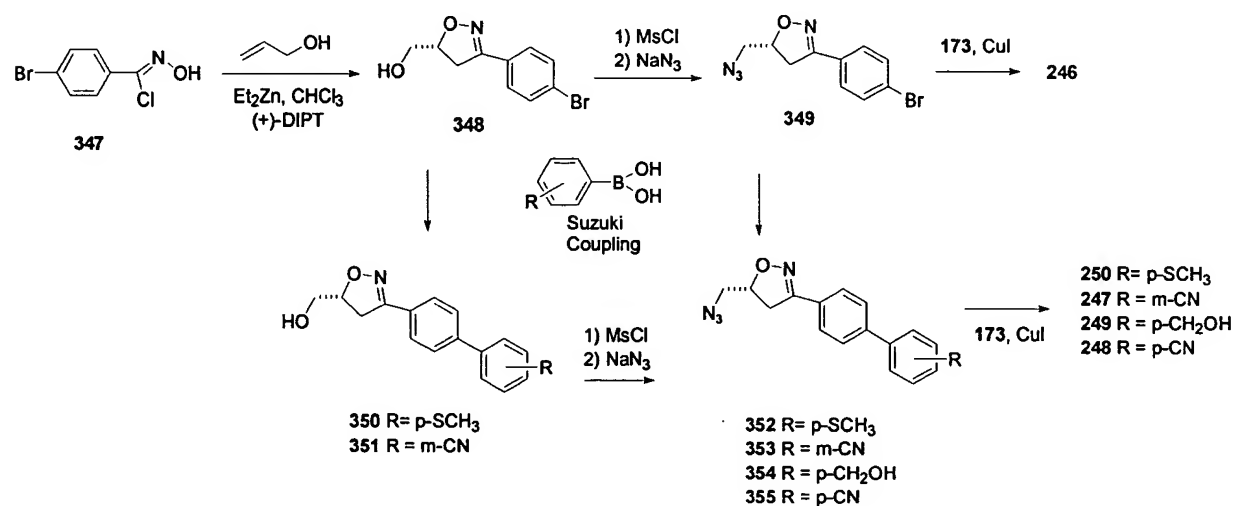
To a solution of alkyne **173** (100 mg, 0.127 mmol) in 4 mL acetonitrile was added **344** (36.3 mg, 0.127 mmol), 2,6-lutidine (0.0163 mL, 0.139 mmol) and CuI (24mg, 0.127 mmol). The mixture was stirred overnight at room temperature, then poured into 10 mL 5% aqueous

NH₃/ice and extracted with ethyl acetate (3x 20 mL). The combined organic extract was washed with water (2x 10 mL), brine (10 mL), dried (Na₂SO₄) and evaporated. The residue was purified by flash-chromatography (eluant: ethyl acetate-MeOH 5:1) yielding **245** (60 mg, 44%). Data for **245**: MS (ESI) *m/z* 1073 (M+H)⁺; ¹HNMR (300 MHz, CDCl₃, partial): δ 7.8 (s, 1H), 7.50-7.30 (m, 3H), 7.21-7.14 (m, 3H), 5.19-4.95 (m, 2H), 4.68-3.90 (m, 7H).

Example 39 – Synthesis of Isoxazolines 246-250

Scheme 62 depicts the synthesis of isoxazolines **246-250**. Hydroxyiminoyl chloride **347** was converted to isoxazoline alcohol **348** as described in the literature (*J. Med. Chem.* **2003**, *46*, 284). The alcohol group of **348** was transformed to the azide **349**, which was treated with alkyne **173** to afford isoxazoline **246**. Azide **349** was coupled to substituted boronic acids to afford azides **354** and **355**, which were treated with alkyne **173** to afford isoxazolines **248** and **249**. Alcohol **348** was coupled to substituted boronic acids to provide alcohols **350** and **351**, which were subsequently converted to azides **352** and **353**. The cycloaddition of **352** and **353** with alkyne **173** gave isoxazolines **250** and **247** respectively.

Scheme 62



Synthesis of azide 349

To a solution of alcohol **348** (2.00 g, 7.81 mmol) in CH₂CH₂ (40 mL) at 0°C was added Et₃N (2.20 mL, 15.6 mmol), followed by the dropwise addition of MsCl (911 μL, 11.7 mmol). The mixture was stirred at 0°C for 30 min, then poured into 30 mL water/ice and extracted with Et₂O (50 mL x 3). The combined organic extract was washed with water (50 mL x 3), dried over

MgSO₄, and evaporated to give 2.70 g of the intermediate mesylate of suitable purity to be used in the next step. The mesylate (2.70 g) was dissolved in DMF (30mL), NaN₃ (2.10 g, 31.238mmol) was added, and the mixture stirred at 80°C for 2.5 h. The mixture was poured into water/ice (150mL) and Et₂O (300mL). The organic extract was washed with water (150mL x 3), dried over MgSO₄, and concentrated to afford azide **349** as a white crystalline solid (2.10 g, 96% yield). Data for **349**: ¹HNMR (300 MHz, CDCl₃): δ 7.54 (s, 4H), 4.93 (dddd, *J* = 10, 8, 5, 5 Hz, 1H), 3.56 (dd, *J* = 13, 5 Hz, 1H), 3.45 (dd, *J* = 13, 5 Hz, 1H), 3.42 (dd, *J* = 17, 11 Hz, 1H), 3.21 (dd, *J* = 17, 7 Hz, 1H).

10 Synthesis of alcohol **350**

A mixture of alcohol **348** (1.00 g, 3.91 mmol), 4-methylthiophenyl boronic acid (1.10 g, 5.86 mmol), palladium acetate (18 mg, 0.078 mmol), 2-(di-tert-butylphosphino)biphenyl (47 mg, 0.156 mmol) and KF (678 mg, 11.7 mmol) in THF (10 mL) at room temperature was degassed by bubbling argon through the mixture. The mixture was then stirred at room temperature for 15 h. The red suspension was poured into 10 mL sat. Na₂CO₃ and 100 mL water. The mixture was extracted with 15% isopropyl alcohol in CH₂CH₂ (200 mL x 3). The combined organic layer was washed with water (100mL x 3), dried over MgSO₄, and evaporated to provide **350** (1.2 g, 100% yield). Data for **350**: ¹HNMR (300 MHz, CDCl₃): δ 7.73 (d, *J* = 8 Hz, 2H), 7.62 (d, *J* = 8 Hz, 2H), 7.55 (d, *J* = 8 Hz, 2H), 7.33 (d, *J* = 8 Hz, 2H), 4.90 (dddd, *J* = 13, 8, 5, 3 Hz, 1H), 3.90 (ddd, *J* = 12, 6, 3 Hz, 1H), 3.71 (ddd, *J* = 12, 8, 5 Hz, 1H), 3.43 (dd, *J* = 17, 11 Hz, 1H), 3.32 (dd, *J* = 17, 8 Hz, 2H), 2.53 (s, 3H), 1.90 (dd, *J* = 8, 6 Hz, 1H).

Synthesis of alcohol **351**

Alcohol **351** was synthesized by the same procedure as reported for alcohol **350** using 3-cyanophenyl boronic acid (956 mg, 5.86 mmol). The mixture was extracted with CH₂CH₂ (100mL x 3). The residue was isolated by flash-chromatography on silica gel (2/100 MeOH/CH₂CH₂ as eluant), to afford alcohol **351** (1.0 g, 92% yield). Data for **351**: ¹HNMR (300 MHz, CDCl₃): δ 7.90-7.77 (m, 4H), 7.69-7.54 (m, 4H), 4.92 (dddd, *J* = 11, 8, 5, 3 Hz, 1H), 3.92 (ddd, *J* = 12, 6, 3 Hz, 1H), 3.72 (ddd, *J* = 12, 8, 5 Hz, 1H), 3.45 (dd, *J* = 17, 11 Hz, 1H), 3.34 (dd, *J* = 17, 8 Hz, 1H), 1.92 (dd, *J* = 8, 6 Hz, 1H).

Synthesis of azide 352

To a suspension of alcohol **350** (2.00 g, 6.68 mmol) in CH₂CH₂ (40 mL) at 0°C was added Et₃N (1.90 mL, 13.4 mmol), and then MsCl (776 µL, 10.0 mmol) dropwise. The mixture was stirred at room temperature for 2 h and then refluxed for 3 h. The mixture was cooled to room temperature and EtOAc/Hexane (150 mL/50 mL) was added. The white solid was collected, washed with water (30 mL x 3), and dried under vacuum to afford 2 g of crude mesylate. The crude mesylate obtained above (0.50 g, 1.33 mmol) was suspended in DMF (8 mL), NaN₃ (348 mg, 5.30 mmol) was added and the mixture stirred at 80°C for 4 h. The mixture was poured into water/ice (50 mL), extracted by EtOAc (30 mL x 4), dried over MgSO₄, the residue was isolated by chromatography on silica gel (40/60 EtOAc/hexane as eluant) to afford azide **352** (305 mg, 71% yield) as a white powder. Data for **352**: ¹HNMR (300 MHz, CDCl₃): δ 7.73 (d, *J* = 8 Hz, 2H), 7.62 (d, *J* = 8 Hz, 2H), 7.55 (d, *J* = 8 Hz, 2H), 7.33 (d, *J* = 8 Hz, 2H), 4.94 (m, 1H), 3.55 (dd, *J* = 13, 5 Hz, 1H), 3.48 (m, 2H), 3.25 (dd, *J* = 17, 7 Hz, 1H), 2.97 (s, 3H).

Synthesis of azide 353

To a solution of alcohol **351** (1.00 g, 3.59 mmol) in CH₂CH₂ (20 mL) at 0°C was added Et₃N (1.00 mL, 7.19 mmol), followed by the dropwise addition of MsCl (419 µL, 5.39 mmol). The mixture was stirred at 0°C for 30 min, and then at room temperature for 2 h. The mixture was poured into 100 mL water/ice and EtOAc/hexane 150 mL/50 mL). The combined organic extract was washed with water (100 mL x 3), dried over MgSO₄, and evaporated to give 1.20 g of the crude mesylate which was used directly in the next step without further purification. The mesylate (1.20 g) was dissolved in DMF (20 mL), and NaN₃ (884 mg, 13.47 mmol) was added, and the mixture was stirred at 80°C for 2.5 h. The mixture was poured into water/ice (150 mL) and EtOAc (250 mL). The organic extract was washed with water (100 mL x 3), dried over MgSO₄, and evaporated. The residue was separated by chromatography on silica gel (30/70 EtOAc/hexane as eluant) to afford azide **353** (836 mg, 77% yield) as a white crystalline solid. Data for **353**: ¹HNMR (300 MHz, CDCl₃): δ 7.90-7.77 (m, 4H), 7.69-7.50 (m, 4H), 4.97 (dddd, *J* = 15, 7, 5, 5 Hz, 1H), 3.57 (dd, *J* = 13, 5 Hz, 1H), 3.50 (m, 2H), 3.26 (dd, *J* = 17, 7 Hz, 1H).

Synthesis of azide 354

A mixture of azide **349** (300 mg, 1.07 mmol), 4-(hydroxymethyl)phenyl boronic acid (286 mg, 1.60 mmol), palladium acetate (5 mg, 0.021 mmol), 2-(di-tert-butylphosphino)biphenyl (13 mg, 0.043 mmol) and KF (188 mg, 3.20 mmol) in THF (4mL) at was degassed by bubbling argon through the mixture. The mixture was then stirred at room temperature for 15 h. The red suspension was poured into 5 mL sat. Na₂CO₃ and 20 mL water. The mixture was extracted with 5% MeOH/CH₂CH₂ (200 mL). The combined organic layer was washed by water (100mL x 3), dried over MgSO₄, and evaporated. The residue was purified by chromatography on silica gel (1.5/100 MeOH/CH₂CH₂ as eluant) to afford azide **354** (220 mg, 67% yield). Data for **354**:
¹HNMR (300 MHz, CDCl₃): δ 7.75 (d, *J* = 8 Hz, 2H), 7.65 (d, *J* = 8 Hz, 2H), 7.62 (d, *J* = 8 Hz, 2H), 7.47 (d, *J* = 8 Hz, 2H), 4.95 (dddd, *J* = 10, 8, 5, 5 Hz, 1H), 4.76 (d, *J* = 6 Hz, 2H), 3.55 (dd, *J* = 13, 5 Hz, 1H), 3.50 (dd, *J* = 17, 11 Hz, 2H), 3.25 (dd, *J* = 17, 7 Hz, 1H), 1.71 (dd, *J* = 5, 5 Hz, 1H).

Synthesis of azide **355**

A mixture of azide **349** (300 mg, 1.07 mmol), 4-cyanophenyl boronic acid (261 mg, 1.60 mmol), palladium acetate (5 mg, 0.021 mmol), 2-(di-tert-butylphosphino)biphenyl (13 mg, 0.043 mmol) and KF (188 mg, 3.20 mmol) in THF (4mL) at room temperature was degassed by bubbling argon through the mixture. The mixture was then stirred at room temperature for 15 h. The red suspension was poured into 5 mL sat. Na₂CO₃ and 20 mL water. The mixture was extracted with CH₂CH₂ (50mL x 3). The combined organic layer was washed by water (100mL x 3), dried over MgSO₄, and evaporated. The residue was purified by chromatography on silica gel (30/70 EtOAc/hexane as eluant) to afford azide **355** (300 mg, 93% yield). Data for **355**:
¹HNMR (300 MHz, CDCl₃): δ 7.83-7.63 (m, 8H), 4.97 (dddd, *J* = 16, 7, 5, 5 Hz, 1H), 3.58 (dd, *J* = 13, 5 Hz, 1H), 3.50 (dd, *J* = 16, 10 Hz, 1H), 3.40 (dd, *J* = 13, 5 Hz, 1H), 3.27 (dd, *J* = 16, 7 Hz, 1H).

General procedure for the synthesis of isoxazolines **246-250**

To a mixture of alkyne **173** (100 mg, 0.127 mmol), the appropriate azide (0.140 mmol, 1.1 eq) in acetonitrile (4.0 mL) at room temperature under argon was added 2,6-lutidine (22 μL, 0.191 mmol, 1.1eq), followed by the addition of copper (I) iodide (12 mg, 0.064 mmol). The mixture was stirred at room temperature for 1.5 to 6 h. After the reaction was complete, 1 mL

5% NH₄OH was added. The mixture was stirred at room temperature for 10 min. The acetonitrile was removed under vacuum. The aqueous phase was extracted with CH₂Cl₂ (30 mL x 3), dried over Na₂SO₄, and evaporated. The residue was purified by chromatography on silica gel (20/80 to 30/70 MeOH/EtOAc) to provide isoxazolines **246** (116mg, 85% yield), **247** (120mg, 87% yield), **248** (120mg, 87% yield), **249** (72mg, 52% yield), and **250** (93mg, 66% yield).

Data for **246**: MS (ESI) *m/z* 1067.6 (M-H)⁺; ¹HNMR (300 MHz, CDCl₃, partial): δ 7.56 (s, 1H), 7.53 (d, *J* = 9 Hz, 2H), 7.74 (d, *J* = 9 Hz, 2H), 5.12 (br s, 1H), 4.71-4.52 (m, 4H), 4.43 (d, *J* = 7 Hz, 1H), 4.29 (br s, 1H), 4.08 (m, 1H), 3.69-3.16 (m, 10H), 3.03 (dd, *J* = 10, 10 Hz, 1H).

Data for **247**: MS (ESI) *m/z* 1090.5 (M)⁺; ¹HNMR (300 MHz, CDCl₃, partial): δ 7.88 (s, 1H), 7.83 (d, *J* = 8 Hz, 1H), 7.75-7.55 (m, 7H), 5.17 (br s, 1H), 5.09 (br s, 1H), 4.80-4.60 (m, 4H), 4.41 (d, *J* = 7 Hz, 1H), 4.26 (br s, 1H), 4.09 (m, 1H), 3.68-3.18 (m, 10H).

Data for **248**: MS (ESI) *m/z* 1090.3 (M)⁺; ¹HNMR (300 MHz, CDCl₃, partial): δ 7.77-7.60 (m, 9H), 5.17 (br s, 1H), 5.09 (br s, 1H), 4.71-4.55 (m, 4H), 4.41 (d, *J* = 7 Hz, 1H), 4.26 (br s, 1H), 4.09 (m, 1H), 3.67-3.20 (m, 4H).

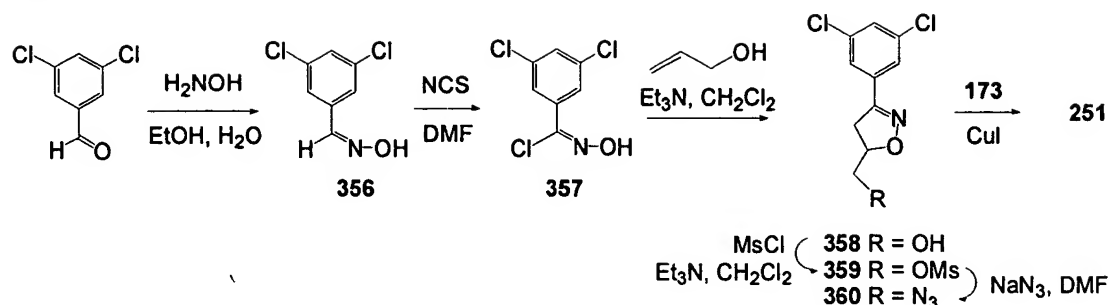
Data for **249**: MS (ESI) *m/z* 1095.4 (M)⁺; ¹HNMR (300 MHz, CDCl₃, partial): δ 7.69-7.57 (m, 7H), 7.46 (d, *J* = 8 Hz, 2H), 5.12 (d, *J* = 4 Hz, 2H), 4.70-4.54 (m, 4H), 4.42 (d, *J* = 7 Hz, 1H), 4.28 (br s, 1H), 4.08 (m, 1H), 3.69-3.20 (m, 10H).

Data for **250**: MS (ESI) *m/z* 1111.4 (M)⁺; ¹HNMR (300 MHz, CDCl₃, partial): δ 7.68-7.50 (m, 7H), 7.35 (d, *J* = 8 Hz, 2H), 5.12 (br s, 1H), 4.71-4.54 (m, 4H), 4.43 (d, *J* = 8 Hz, 1H), 4.29 (br s, 1H), 4.07 (m, 1H), 3.69-3.20 (m, 10H), 3.03 (dd, *J* = 10, 10 Hz, 1H).

Example 40 – Synthesis of Isoxazolines **251** and **252**

Scheme 63 depicts the synthesis of isoxazoline **251**. Hydroxyiminoyl chloride **357** was made from the oxime (**356**) of 3,5-dichlorobenzaldehyde. The cycloaddition of **357** and allyl alcohol (via the intermediate nitrile oxide) afforded racemic isoxazoline alcohol **358**. The alcohol was converted to azide **360** via the mesylate **359**. The cycloaddition of **360** with alkyne **173** yielded isoxazoline **251** (as a diastereomeric mixture). Isoxazoline **252** was synthesized (also as a diastereomeric mixture) by carrying 3,5-difluorobenzaldehyde through the sequence of Scheme 63.

Scheme 63



5 Synthesis of oxime 356

A solution of 3,5-dichlorobenzaldehyde (2.0 g, 11.42 mmol) and hydroxylamine hydrochloride (0.87 g, 12.57 mmol) in ethanol (40 mL) and water (80 mL) was cooled to 4°C, and NaOH (50%(w/w), 2.3 mL) was added. The reaction mixture was stirred for 3 h at room temperature. The reaction mixture was then neutralized to pH 6.0, and partitioned with methylene chloride and water. The aqueous layer was extracted twice with methylene chloride, and the combined organic layer was washed with brine, dried (Na₂SO₄), and evaporated to yield **356** (2.15 g, 99% yield) as a white solid. Data for **356**: ¹HNMR (300 MHz, CDCl₃): δ 8.11 (s, 1H), 7.45 (s, 1H), 7.34 (s, 1H).

15 Synthesis of hydroximinoyl chloride 357

To a solution of oxime **356** (2.15 g, 11.31 mmol) in dimethylformamide (10 mL) was added *N*-chlorosuccinimide (1.5 g, 11.31 mmol). The reaction mixture was warmed to 50°C for 1 h. The reaction was then diluted with ethyl acetate (50 mL), and washed with brine, dried (Na₂SO₄), and evaporated to yield **357** (2.60 g, 100% yield). Data for **357**: ¹HNMR (300 MHz, CDCl₃): δ 7.8 (s, 1H), 7.50 (s, 1H), 7.17 (s, 1H).

Synthesis of isoxazoline alcohol 358

To a solution of hydroximinoyl chloride **357** (1.50 g, 6.68 mmol) in methylene chloride (50 mL) was added allyl alcohol (0.45 mL, 6.68 mmol). The mixture was cooled to 0°C, and triethylamine (1.0 mL, 6.68 mmol) was added. The reaction mixture was slowly warmed to room temperature, stirred for 16 h, quenched with water (50 mL), and extracted twice with

methylene chloride. The combined organic layer was washed with brine, dried over Na₂SO₄, and evaporated to yield **358** (1.60 g, 100% yield). Data for **358**: ¹HNMR (300 MHz, CDCl₃): δ 7.47 (s, 2H), 7.32 (s, 1H), 4.84 (m, 1H), 3.82 (dd, *J* = 15, 3 Hz, 1H), 3.62 (dd, *J* = 16, 4 Hz, 1H), 3.23 (m, 2H).

5

Synthesis of mesylate **359**

Alcohol **358** (1.60 g, 6.50 mmol) was dissolved in 5 mL methylene chloride, and the mixture cooled to 0°C. Triethylamine (1.8 mL, 13.0 mmol) was added, followed by methanesulfonyl chloride (0.7 mL, 9.10 mmol). The mixture was allowed to warm to room temperature and stirred for 1 h. Methylene chloride (20 mL) was added, and the mixture washed twice with 1N HCl, then twice with 10% aqueous sodium carbonate, and then brine. The organic phase was dried (Na₂SO₄), and evaporated to yield mesylate **359** (1.60 g, 99% yield). Data for **359**: ¹HNMR (300 MHz, CDCl₃): δ 7.67 (s, 2H), 7.56 (s, 1H), 5.22 (m, 1H), 4.51 (m, 2H), 3.60 (m, 1H), 3.40 (dd, *J* = 7, 15 Hz, 1H), 3.25 (s, 3H).

15

Synthesis of azide **360**

A solution of mesylate **359** (1.60 g, 6.15 mmol) in dimethylformamide (10 mL) was treated with sodium azide (1.6 g, 24.60 mmol) and the mixture heated to 80°C for 3 h. The reaction mixture was cooled to room temperature, diluted with ethyl acetate (50 mL), and washed with brine (2 x 50 mL). Drying (Na₂SO₄), and evaporation provided azide **360** (1.28, 77% yield) as a yellow oil of suitable purity for use in subsequent reactions. Data for **360**: ¹HNMR (300 MHz, CDCl₃): δ 7.45 (s, 2H), 7.39 (s, 1H), 3.51 (dd, *J* = 17, 4 Hz, 1H), 3.35-3.20 (m, 2H), 3.13 (m, 1H).

25 Synthesis of isoxazoline **251**

A solution of alkyne **173** (170 mg, 0.220 mmol) in tetrahydrofuran (10 mL) was treated with azide **360** (0.08 g, 0.324 mmol), *N,N*-diisopropylethylamine (0.05 mL, 0.22 mmol) and copper (I) iodide (0.03 g, 0.160 mmol), and the mixture was stirred under argon at room temperature for 16 h. The reaction mixture was diluted with ethyl acetate (50 mL), and washed with brine (2 x 50 mL). The organic phase was dried and evaporated. The residue was purified by preparative thin layer chromatography (using 80% CH₂Cl₂, 20% MeOH, 1% NH₄OH as

eluant) to provide isoxazoline **251** (197 mg, 86% yield) as a yellow solid. Data for **251**: ¹H-NMR (300 MHz, CDCl₃, partial): δ 7.36 (s, 2H), 7.22 (s, 1H), 4.96 (m, 2H), 4.24 (m, 2H), 4.10 (m, 1H), 3.52-3.15 (m, 2H), 3.06 (s, 1H), 2.59 (m, 2H).

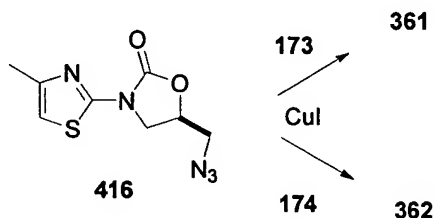
5 Synthesis of isoxazoline **252**

This compound was made from alkyne **173** and the requisite 3,5-difluoro azide using the same procedures reported above for the synthesis of isoxazoline **251**. Data for **252**: ¹H-NMR (300 MHz, CDCl₃, partial): δ 7.50 (s, 1H), 7.10 (d, *J* = 3 Hz, 2H), 6.86 (m, 1H), 5.10 (m, 1H), 5.08 (m, 1H), 4.66 (m, 1H), 4.61 (m, 2H), 4.41 (m, 1H), 4.20 (m, 1H), 4.10 (m, 1H), 3.68 (m, 2H), 3.32-3.22 (m, 2H), 2.84 (t, 2H).

Example 41 – Synthesis of Triazoles 361-367

Scheme 64 depicts the synthesis of triazoles **361** and **362**. Azide **416** was treated with alkynes **173** and **174** to produce triazoles **361** and **362** respectively.

Scheme 64



Synthesis of azide **416**

Azide **416** was synthesized from 2-amino-3-methyl-thiazole using the chemistry reported in the literature (Brickner, S.J. *et al. J. Med. Chem.* 1996, 39, 673). Data for **416**: ¹H-NMR (300 MHz, CDCl₃): δ 6.59 (s, 1H), 4.92-4.87 (m, 1H), 4.34 (t, *J* = 9 Hz, 1H), 4.12 (dd, *J* = 6, 3 Hz, 1H), 3.73 (dd, *J* = 3, 12 Hz, 1H), 3.61 (dd, *J* = 3, 12 Hz, 1H), 2.35 (s, 3H).

25 Synthesis of triazole **361**

To a mixture of alkyne **173** (150 mg, 0.191 mmol), azide **416** (55 mg, 0.229 mmol) and copper (I) iodide (18.3 mg, 0.096 mmol) was added THF (10 mL) and the mixture was repeatedly degassed and flushed with argon. Then *i*-Pr₂NEt (0.05 mL) was introduced and the

mixture was stirred at room temperature for 1 h. The reaction mixture was poured into NH_4Cl (30 mL) and stirred for few minutes. Then NH_4OH (3 mL) was added and the mixture was extracted with methylene chloride (3 x 40 mL). The combined organic layer was dried (Na_2SO_4), concentrated and flash chromatographed over silica gel (methylene chloride: MeOH : NH_4OH = 12:1:0.025) to provide 150 mg of the product. Data for **361**: MS (ESI) m/z 514 ($\text{M}+2\text{H}$)²⁺; ¹H NMR (300 MHz, CDCl_3 , partial): δ 7.59 (s, 1H), 6.56 (s, 1H), 5.22-5.10 (m, 2H), 4.79-4.62 (m, 4H), 4.46-4.39 (m, 2H), 4.28 (br d, J = 3 Hz, 1H), 0.91-0.87 (m, 6H).

Synthesis of triazole **362**

The cycloaddition of alkyne **174** (150 mg, 0.187 mmol) and azide **416** (49.2 mg, 0.206 mmol) was performed under similar conditions as described above for the synthesis of **361** to afford 169 mg of **362**. Data for **362**: MS (ESI) m/z 521 ($\text{M}+2\text{H}$)²⁺; ¹H NMR (300 MHz, CDCl_3 , partial): δ 7.49 (s, 1H), 6.56 (s, 1H), 5.18-5.12 (m, 2H), 3.34 (s, 3H), 3.03 (t, J = 9 Hz, 1H), 0.91-0.87 (m, 6H).

Synthesis of triazole **363**

Triazole **363** (117 mg) was synthesized from alkyne **174** (100 mg, 0.125 mmol) and azide **189** (29.7 mg, 0.126 mmol) following the same procedure as described above for compound **361**. Data for **363**: MS (ESI) m/z 519 ($\text{M}+2\text{H}$)²⁺; ¹H NMR (300 MHz, CDCl_3 , partial): δ 7.52 (s, 1H), 7.35-7.28 (m, 2H), 7.08 (br d, J = 8 Hz, 1H), 6.84 (dd, J = 2, 8 Hz, 1H), 5.10-5.01 (m, 2H), 4.29 (d, J = 3 Hz, 1H), 3.23 (t, J = 8 Hz, 1H), 3.03 (t, J = 9 Hz, 2H), 0.91-0.87 (m, 6H).

Synthesis of triazole **364**

Triazole **364** (141 mg) was synthesized from alkyne **174** (150 mg, 0.187 mmol) and azide **277** (57.5 mg, 0.206 mmol) following the same procedure as described above for compound **361**. Data for **364**: MS (ESI) m/z 541 ($\text{M}+2\text{H}$)²⁺; ¹H NMR (300 MHz, CDCl_3 , partial): δ 7.52 (s, 1H), 7.22 (d, J = 2 Hz, 1H), 6.93 (dd, J = 2, 8 Hz, 1H), 6.83 (t, J = 9 Hz, 1H), 5.09 (d, J = 5 Hz, 1H), 5.05-4.98 (m, 1H), 4.45 (d, J = 7 Hz, 1H), 3.88 (dd, J = 6, 3 Hz, 1H), 3.34 (s, 3H), 3.03 (t, J = 9 Hz, 1H), 0.91-0.87 (m, 6H).

Synthesis of triazole 365

Triazole **365** (200 mg) was synthesized from alkyne **174** (150 mg, 0.187 mmol) and azide **266** (63.6 mg, 0.206 mmol) following the same procedure as described above for compound **361**. Data for **365**: MS (ESI) m/z 556 ($M+2H$)²⁺; ¹H NMR (300 MHz, CDCl₃, partial): δ 7.52 (s, 1H), 7.28-7.23 (m, 1H), 6.98-6.91 (m, 2H), 5.12 (d, J = 5 Hz, 1H), 5.04-5.02 (m, 1H), 4.45 (d, J = 7 Hz, 1H), 4.28 (br d, J = 3 Hz, 1H), 4.13-4.05 (m, 2H), 3.88 (dd, J = 6, 3 Hz, 1H), 3.74 (t, J = 5 Hz, 2H), 3.34 (s, 3H), 3.03 (t, J = 9 Hz, 1H), 0.91-0.87 (m, 6H).

Synthesis of triazole 366

The required 3,5-difluorophenyl oxazolidinone azide was synthesized from 3,5-difluoroaniline using the same procedure as that used for the synthesis of azide **189**. Triazole **366** (157 mg) was synthesized from alkyne **174** (150 mg, 0.187 mmol) and the 3,5-difluorophenyl oxazolidinone azide (52.3 mg, 0.206 mmol) following the same procedure as described above for compound **361**. Data for **366**: MS (ESI) m/z 528.6 ($M+2H$)²⁺, 1055.8 ($M+H$)⁺; ¹H NMR (300 MHz, CDCl₃, partial): δ 7.50 (s, 1H), 7.02 (dd, J = 2, 9 Hz, 2H), 6.62-6.55 (m, 1H), 5.14 (d, J = 5 Hz, 1H), 5.10-5.02 (m, 1H), 4.81 (d, J = 6 Hz, 1H), 4.72 (d, J = 4 Hz, 2H), 4.45 (d, J = 7 Hz, 1H), 3.93 (dd, J = 6, 3 Hz, 1H), 3.34 (s, 3H), 3.23 (dd, J = 7, 3 Hz, 1H), 3.03 (t, J = 10 Hz, 1H), 0.91-0.86 (m, 6H).

Synthesis of triazole 367

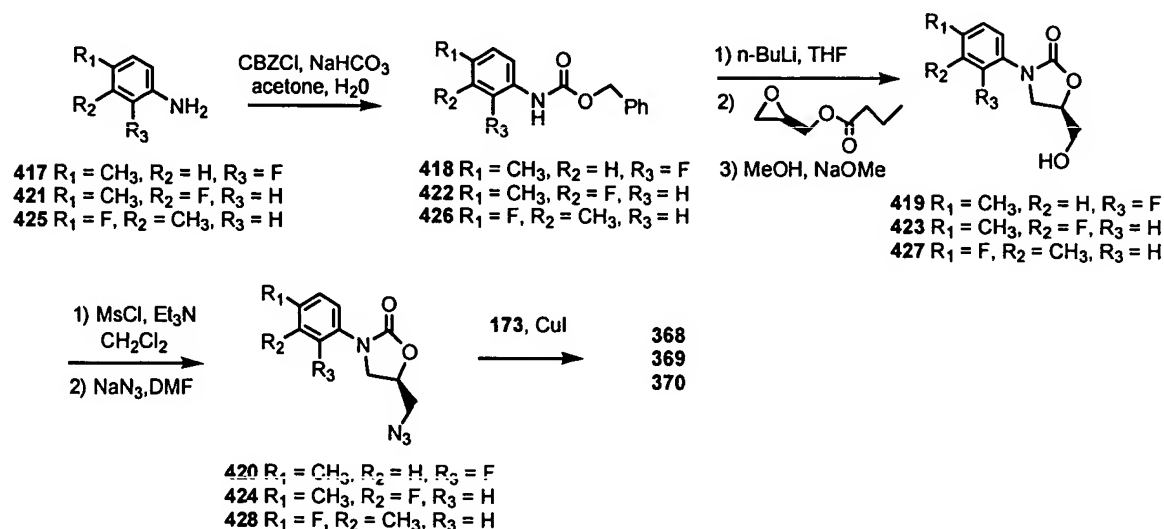
Triazole **367** (200 mg) was synthesized from alkyne **174** (150 mg, 0.187 mmol) and azide **323** (59.1 mg, 0.206 mmol) following the same procedure as described above for compound **361**. Data for **367**: MS (ESI) m/z 545 ($M+2H$)²⁺; ¹H NMR (300 MHz, CDCl₃, partial): δ 7.58 (d, J = 3 Hz, 1H), 7.50 (s, 1H), 7.40 (d, J = 9 Hz, 1H), 7.28-7.24 (m, 1H), 5.14 (d, J = 4 Hz, 1H), 5.10-5.02 (m, 1H), 4.44 (d, J = 7 Hz, 1H), 4.29 (br d, J = 2 Hz, 1H), 3.95 (dd, J = 6, 3 Hz, 1H), 3.34 (s, 3H), 3.23 (dd, J = 7, 3 Hz, 1H), 3.03 (t, J = 9 Hz, 1H), 0.91-0.86 (m, 6H).

Example 42 – Synthesis of Triazoles 368-370

Scheme 65 depicts the synthesis of triazoles **368-370**. The required azides **420**, **424**, and **428** were synthesized using standard methods from the appropriate anilines. The cycloaddition of these azides with alkyne **173** afforded triazoles **368-370**.

5

Scheme 65



Synthesis of azides **420**, **424**, **428**

The azides were synthesized from the substituted anilines using the chemistry reported in the literature (Brickner, S.J. *et al. J. Med. Chem.* **1996**, *39*, 673).

Data for **420**: MS (ESI) m/z 291.9 ($\text{M}+\text{H}+\text{CH}_3\text{CN}$)⁺, ¹H-NMR, (300 MHz, CDCl₃): δ 7.31 (t, $J = 8$ Hz, 1H), 6.96-6.91 (m, 2H), 4.76 (m, 1H), 4.01 (t, $J = 9$ Hz, 1H), 3.73 (m, 1H), 3.63 (dd, $J = 13, 4$ Hz, 1H), 3.50 (dd, $J = 14, 5$ Hz, 1H), 2.31 (s, 3H).

Data for **424**: ¹H-NMR, (300 MHz, CDCl₃): δ 7.28 (dd, $J = 12, 2$ Hz, 1H), 7.08-7.00 (m, 2H), 4.71 (m, 1H), 3.98 (t, $J = 9$ Hz, 1H), 3.74 (m, 1H), 3.63 (dd, $J = 13, 4$ Hz, 1H), 3.50 (dd, $J = 14, 5$ Hz, 1H), 2.16 (d, $J = 2$ Hz, 3H).

Data for **428**: ¹H-NMR, (300 MHz, CDCl₃) δ 7.29 (m, 1H), 7.19 (m, 1H), 6.92 (t, $J = 9$ Hz, 1H), 4.69 (m, 1H), 3.98 (t, $J = 9$ Hz, 1H), 3.75 (m, 1H), 3.62 (dd, $J = 13, 4$ Hz, 1H), 3.50 (dd, $J = 13, 5$ Hz, 1H), 2.21 (s, 3H).

20

Synthesis of triazole 368

This compound was obtained from the reaction of alkyne **173** (0.115 g, 0.148 mmol) with azide **420** (0.048 g, 0.192 mmol) in the presence of CuI (0.023 g, 0.111 mmol) in THF (5 mL) and Hunig's base (0.05 mL) at room temperature within 30 min. The reaction was poured into a mixture containing saturated NH₄Cl/NH₄OH (pH = 9.5, 30 mL) and extracted with CH₂Cl₂ (3 x 30 mL). The combined organic layer was dried over Na₂SO₄ and the solvent evaporated. The crude was purified on silica gel eluting with CH₂Cl₂/MeOH/NH₄OH 18:1:0.05 to 15:1:0.05 to 12:1:0.05 to give **368** as a white solid (0.146 g, 95% yield). Data for **368**: MS (ESI) *m/z* 1037.1 (M + H)⁺; ¹H-NMR (300 MHz, CDCl₃, partial): δ 7.59 (s, 1H), 7.05 (t, *J* = 8 Hz, 1H), 6.89-6.84 (m, 2H), 5.02 (m, 2H), 4.37 (d, *J* = 7 Hz, 1H), 4.22 (d, *J* = 2 Hz, 1H), 4.07 (m, 2H), 3.78 (m, 1H), 3.60 (m, 2H), 0.82 (m, 6H).

Synthesis of triazole 369

This compound was obtained from the reaction of alkyne **173** (0.115 g, 0.148 mmol) with azide **424** (0.048 g, 0.192 mmol) in the presence of CuI (0.023 g, 0.111 mmol) in THF (5 mL) and Hunig's base (0.02 mL) at room temperature within 30 min. The reaction was worked-up as described for the synthesis of **368** and purified on silica gel eluting with CHCl₃/MeOH/NH₄OH 15:1:0.05 to give **369** as a white solid (0.121 g, 79% yield). Data for **369**: MS (ESI) *m/z* 1037.8 (M + H)⁺; ¹H-NMR (300 MHz, CDCl₃, partial): δ 7.61 (s, 1H), 7.24 (m, 1H), 7.11 (t, *J* = 8 Hz, 1H), 6.95 (m, 1H), 5.08 (d, *J* = 4 Hz, 1H), 5.02 (m, 1H), 4.69 (m, 3H), 4.57 (m, 1H), 4.42 (d, *J* = 7 Hz, 1H), 4.27 (d, *J* = 3 Hz, 1H), 4.10 (m, 2H), 3.91 (m, 1H), 3.65 (m, 2H), 0.88 (m, 6H).

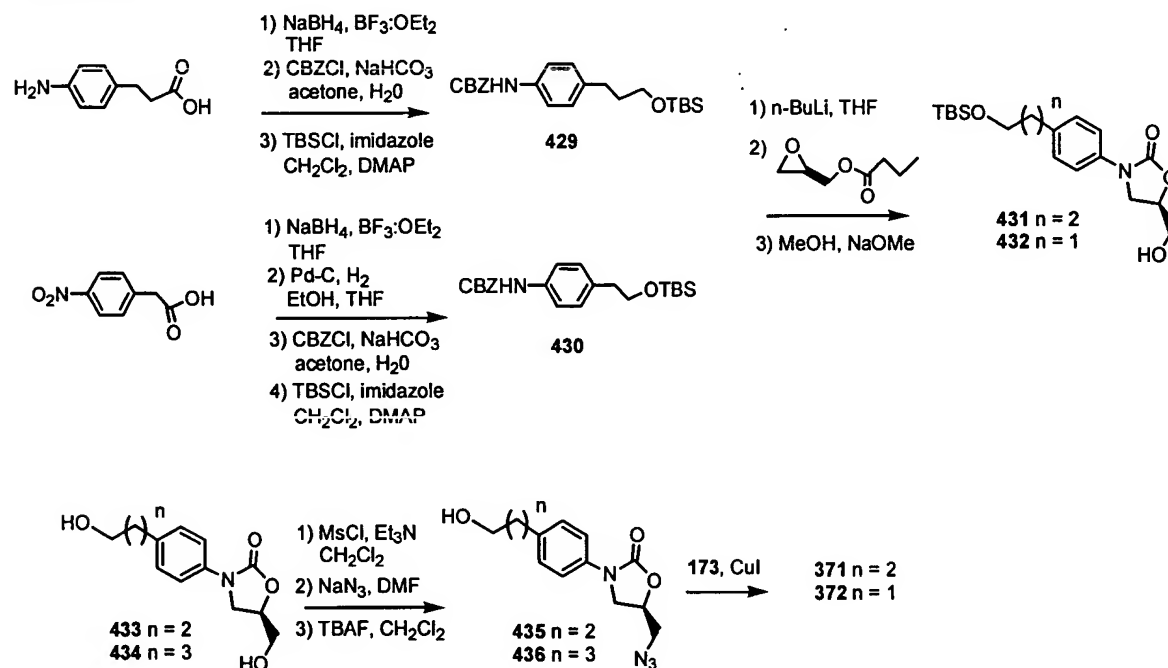
Synthesis of triazole 370

This compound was obtained from the reaction of alkyne **173** (0.115 g, 0.148 mmol) with azide **428** (0.048 g, 0.192 mmol) in the presence of CuI (0.023 g, 0.111 mmol) in THF (5 mL) and Hunig's base (0.02 mL) at room temperature within 30 min. The reaction was worked-up as described for the synthesis of **368** and purified on silica gel eluting with CHCl₃/MeOH/NH₄OH 15:1:0.05 to give **370** as a white solid (0.129 g, 84% yield). Data for **370**: MS (ESI) *m/z* 1037.8 (M + H)⁺; ¹H-NMR (300 MHz, CDCl₃, partial): δ 7.62 (s, 1H), 7.23-7.16 (m, 2H), 6.98 (t, *J* = 9 Hz, 1H), 5.08-5.04 (m, 2H), 4.72 (m, 3H), 4.44 (d, *J* = 7 Hz, 1H), 4.29 (m, 2H), 4.11 (m, 2H), 3.93 (m, 1H), 3.66 (m, 2H), 0.90 (m, 6H).

Example 43 – Synthesis of Triazoles 371 and 372

Scheme 66 depicts the synthesis of triazoles **371** and **372**. The silylethers **429** and **430** were synthesized from the available carboxylic acids, and were transformed into azides **435** and **436**. The cycloaddition of **435** and **436** yielded triazoles **371** and **372** respectively.

Scheme 66



10 Synthesis of silylethers **429** and **430**

3-(4-Amino-phenyl)-propionic acid was reduced to the corresponding amino alcohol as described in the literature (Anhowry *et al.*, *J. Chem. Soc. Perkin Trans. I* **1974**, 191-192). The crude amino alcohol was sequentially protected with CBZ- and TBS-groups as described below for compound **437**. The crude was purified on silica gel (eluting with EtOAc/Hexanes, 1:7) to give compound **429** as colorless oil (about 74% yield, three steps).

(4-Nitro-phenyl)-acetic acid was reduced to the nitro-alcohol as described in the literature (Anhowry *et al.*, *J. Chem. Soc. Perkin Trans. I* **1974**, 191-192). Catalytic hydrogenation afforded the corresponding amino alcohol. Subsequent CBZ- and TBS-group protection, as described below for compound **437**, followed by purification on a silica gel column (eluting with EtOAc/Hexanes, 1:8 to 1:7) gave compound **430** as white solid (about 78% yield, 4 steps).

Synthesis of azides 435 and 436

Silylethers **429** and **430** were converted to azides **435** and **436** using the chemistry reported in the literature (Brickner, S.J. *et al. J. Med. Chem.* **1996**, *39*, 673), followed by
5 desilylation using standard conditions.

Synthesis of triazoles 371 and 372

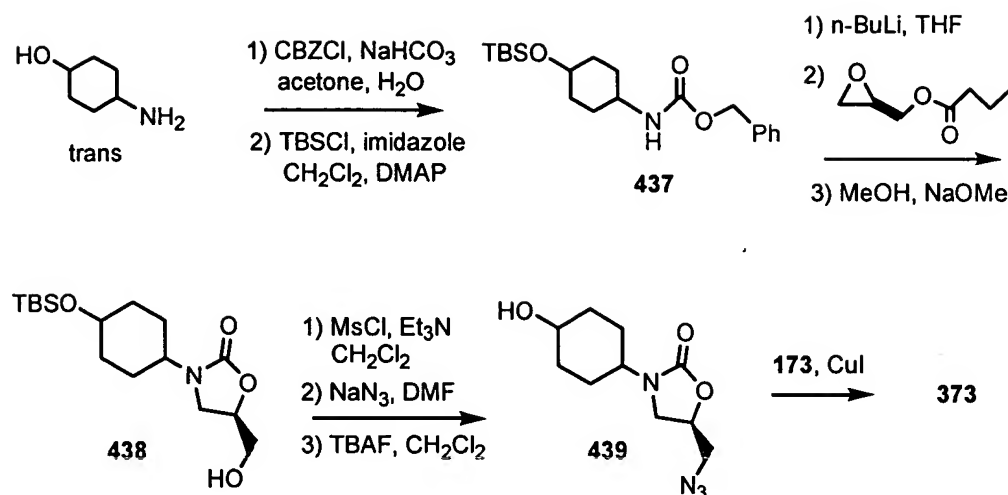
Triazole **371** was obtained from the reaction of alkyne **173** (0.120 g, 0.154 mmol) with
azide **435** (0.051 g, 0.185 mmol) in the presence of CuI (0.023 g, 0.111 mmol) in THF (5 mL)
10 and Hunig's base (0.02 mL) at room temperature within 30 min. The reaction was worked-up as
described for the synthesis of triazole **368** and purified on silica gel (eluting with CH₂Cl₂/
MeOH/NH₄OH 15:1:0.05 to 14:1:0.05) to give **371** as a white solid (0.124 g, 76 % yield). Data
for **371**: MS (ESI) *m/z* 1063.9 (M + H)⁺; ¹H-NMR (300 MHz, CDCl₃, partial): δ 7.63 (s, 1H),
7.32 (d, *J* = 8 Hz, 2H), 7.19 (d, *J* = 8 Hz, 2H), 5.05 (m, 2H), 4.72 (m, 3H), 4.45 (d, *J* = 7 Hz,
15 2H), 4.28 (d, *J* = 4 Hz, 1H), 4.15 (m, 2H), 3.92 (m, 1H), 0.90 (m, 6H).

Triazole **372** was obtained from the reaction of alkyne **173** (0.120 g, 0.154 mmol) with
azide **436** (0.049 g, 0.185 mmol) in the presence of CuI (0.023 g, 0.111 mmol) in THF (5 mL)
and Hunig's base (0.02 mL) at room temperature within 30 min. The reaction was worked-up as
described for the synthesis of triazole **368** and purified on silica gel (eluting with CH₂Cl₂/
20 MeOH/NH₄OH 15:1:0.05 to 14:1:0.05) to give **372** as a white solid (0.116 g, 72 % yield). Data
for **372**: MS (ESI) *m/z* 1050.0 (M + H)⁺; ¹H-NMR (300 MHz, CDCl₃, partial): δ 7.59 (s, 1H),
7.31 (d, *J* = 8 Hz, 2H), 7.18 (d, *J* = 8 Hz, 2H), 5.02 (m, 2H), 4.66 (m, 3H), 4.51 (m, 1H), 4.40 (d,
J = 6 Hz, 2H), 4.24 (m, 1H), 4.10 (m, 2H), 3.61 (m, 2H), 0.86 (m, 6H).

25 Example 44 – Synthesis of Triazole 373

Scheme 67 depicts the synthesis of triazole **373**. Trans 4-aminocyclohexanol was
converted to carbamate **437** prior to further manipulation into azide **439**. The cycloaddition of
439 with alkyne **173** afforded triazole **373**.

30 Scheme 67



Synthesis of carbamate 437

- Trans 4-aminocyclohexanol was protected with a CBZ-group as described in the literature (Brickner, S. J. *et al. J. Med. Chem.* **1996**, 39, 673) and protected with a TBS-group as described in the literature (Green, T. W.; Wuts, P.G. M., *Protective Groups in Organic Synthesis*, 1991, John Wiley & Sons, Inc., pp 77- 83) to give crude compound **437** which was used without further purification.

10 Synthesis of azide 439

Carbamate **437** was converted to azide **439** using the chemistry reported in the literature (Brickner, S.J. *et al. J. Med. Chem.* **1996**, 39, 673).

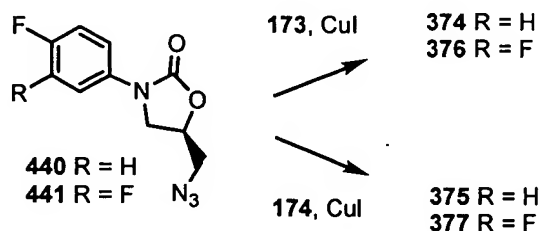
Synthesis of triazole 373

- Triazole **373** was obtained from the reaction of alkyne **173** (0.140 g, 0.180 mmol) with azide **439** (0.050 g, 0.210 mmol) in the presence of CuI (0.023 g, 0.111 mmol) in THF (5 mL) and Hunig's base (0.05 mL) at room temperature within 30 min. The reaction was worked-up as described for the synthesis of triazole **368** and purified on silica gel (eluting with CH₂Cl₂/MeOH/NH₄OH 14:1:0.075) to give triazole **373** as a white solid (0.135 g, 73 % yield). Data for **373**: MS (ESI) *m/z* 1027.8 (M + H)⁺; ¹H-NMR (300 MHz, CDCl₃, partial): δ 7.50 (s, 1H), 5.13 (m, 2H), 4.90 (m, 2H), 4.61 (m, 4H), 4.12 (m, 3H), 0.90 (m, 6H).

Example 45 – Synthesis of Triazoles 374-377

Scheme 68 depicts the synthesis of triazoles **374-377**. The cycloaddition of fluoroaryl azides **440** and **441** with alkynes **173** and **174** provided triazoles **374-377**.

5 Scheme 68



Synthesis of azides **440** and **441**

10 The azides were synthesized from the substituted anilines using the chemistry reported in the literature (Brickner, S.J. *et al. J. Med. Chem.* 1996, 39, 673).

Synthesis of triazole **374**

15 This compound was obtained from the reaction of alkyne **173** (0.250 g, 0.318 mmol) with azide **440** (0.090 g, 0.381 mmol) in the presence of CuI (0.031 g, 0.150 mmol) in THF (10 mL) and Hunig's base (0.1 mL) at room temperature within 30 min. The reaction was worked-up as described for the synthesis of **368** and purified on silica gel eluting with CH₂Cl₂/MeOH/NH₄OH 15:1:0.05 to give **374** as a white solid (0.294 g, 90% yield). Data for **374**: MS (ESI) *m/z* 1023.7 (M + H)⁺; ¹H-NMR (300 MHz, CDCl₃, partial): δ 7.55 (s, 1H), 7.30 (m, 2H), 6.97 (t, *J* = 9 Hz, 2H), 4.99 (m, 2H), 4.36 (d, *J* = 7 Hz, 1H), 4.22 (d, *J* = 3 Hz, 1H), 4.07 (m, 2H), 3.84 (m, 1H),
20 3.59 (m, 2H), 0.82 (m, 6H).

Synthesis of triazole **375**

25 This compound was obtained from the reaction of alkyne **174** (0.150 g, 0.187 mmol) with azide **440** (0.068 g, 0.288 mmol) in the presence of CuI (0.023 g, 0.111 mmol) in THF (5 mL) and Hunig's base (0.05 mL) at room temperature within 30 min. The reaction was worked-up as described for the synthesis of **368** and purified on silica gel eluting with CH₂Cl₂/MeOH/NH₄OH 15:1:0.05 to 12:1:0.05 to give **375** as a white solid (0.139 g, 72% yield). Data for **375**: MS (ESI) *m/z* 1037.7 (M + H)⁺; ¹H-NMR (300 MHz, CDCl₃): δ 7.46 (s, 1H), 7.27 (m, 2H), 6.97 (m, 2H),

5.05 (d, $J = 5$ Hz, 1H), 4.96 (m, 1H), 4.65 (m, 4H), 4.38 (d, $J = 7$ Hz, 1H), 4.22 (d, $J = 3$ Hz, 1H), 4.05 (m, 2H), 3.87 (m, 1H), 3.56 (m, 2H), 0.83 (m, 6H).

Synthesis of triazole 376

5 This compound was obtained from the reaction of alkyne **173** (0.140 g, 0.180 mmol) with azide **441** (0.053 g, 0.210 mmol) in the presence of CuI (0.023 g, 0.111 mmol) in THF (5 mL) and Hunig's base (0.05 mL) at room temperature within 30 min. The reaction was worked-up as described for the synthesis of **368** and purified on silica gel eluting with CH₂Cl₂/MeOH/NH₄OH 15:1:0.05 to 15:1:0.1 to give **376** as a white solid (0.183 g, 98% yield). Data for **376**: MS (ESI) m/z 1041.7 ($M + H$)⁺; ¹H-NMR (300 MHz, CDCl₃, partial): δ 7.61 (s, 1H), 7.48 (m, 1H), 7.13 (m, 1H), 7.00 (m, 1H), 5.07 (m, 2H), 4.72 (m, 3H), 4.43 (d, $J = 7$ Hz, 1H), 4.29 (m, 2H), 4.14 (m, 2H), 3.85 (m, 1H), 3.66 (m, 2H), 0.88 (m, 6H).

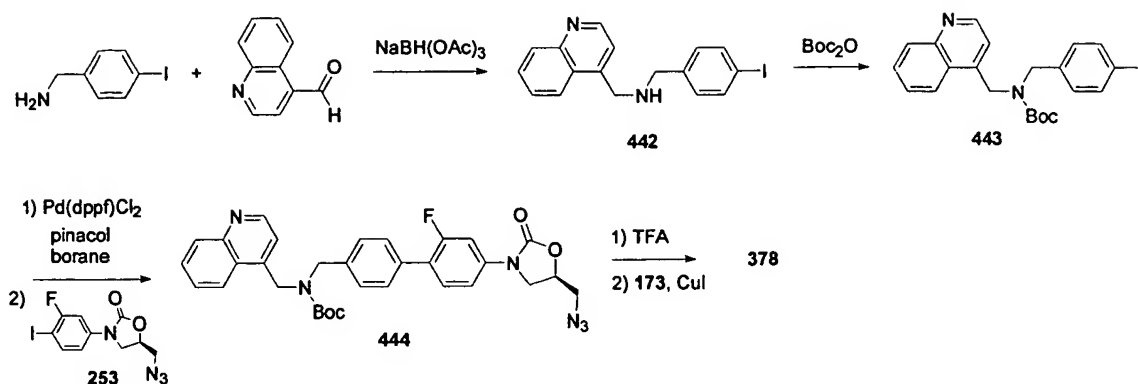
Synthesis of triazole 377

15 Alkyne **174** (150 mg, 0.187 mmol) and azide **441** (52.3 mg, 0.206 mmol) were treated with copper (I) iodide under similar conditions as reported above for the synthesis of triazole **361** to afford 170 mg of **377**. Data for **377**: MS (ESI) m/z 528.5 ($M+2H$)²⁺, 1055.7 ($M+H$)⁺; ¹H NMR (300 MHz, CDCl₃, partial): δ 7.51 (s, 1H), 7.49-7.42 (m, 1H), 7.14 (dd, $J = 9, 9$ Hz, 1H), 6.99-6.96 (m, 1H), 5.13 (d, $J = 5$ Hz, 1H), 5.07-5.02 (m, 1H), 4.44 (d, $J = 7$ Hz, 1H), 3.95 (dd, $J = 6, 3$ Hz, 1H), 3.48 (s, 3H), 3.34 (s, 3H), 3.03 (t, $J = 9$ Hz, 1H), 0.92-0.87 (m, 6H).

Example 46 – Synthesis of Triazole 378

Scheme 69 depicts the synthesis of triazole **378**. The reductive amination reaction of 4-iodobenzylamine and quinoline-4-carboxaldehyde yielded amine **442** which was converted to the BOC derivative **443**. Palladium-catalyzed conversion of iodide **443** to the corresponding pinacol boronate ester was followed by *in situ* Suzuki coupling with iodoaryl azide **253** to yield azide **444**. The cycloaddition of **444** with alkyne **173** gave triazole **378**.

Scheme 69



Synthesis of amine 442

A solution of 4-iodobenzylamine (0.93 g, 4.0 mmol) in methanol (10 mL) was treated
 5 with quinoline-4-carboxaldehyde (0.50 g, 3.2 mmol), acetic acid (0.2 mL) and sodium
 triacetoxyborohydride (1.7 g, 8.0 mmol), and the mixture was stirred under argon at 23°C for 3
 h. The reaction mixture was diluted with ethyl acetate (150 mL), washed with saturated aqueous
 sodium bicarbonate (2 × 100 mL), dried (Na₂SO₄), and evaporated to provide iodide **442** (0.83
 mg, 69% yield) as a yellow oil. Data for **442**: MS (ESI) *m/z* 375 (M+H)⁺; ¹HNMR (300 MHz,
 10 CDCl₃): δ 8.80 (d, *J* = 5 Hz, 1H), 8.07 (d, *J* = 8 Hz, 1H), 7.94 (d, *J* = 8 Hz, 1H), 7.65–7.58 (m,
 1H), 7.59 (d, *J* = 8 Hz, 2H), 7.52–7.42 (m, 1H), 7.37 (d, *J* = 5 Hz, 1H), 7.05 (d, *J* = 8 Hz, 2H),
 4.13 (s, 2H), 3.76 (s, 2H).

Synthesis of iodide 443

15 A solution of iodide **442** (0.66 g, 1.8 mmol) in methylene chloride (15 mL) was treated
 with di-*tert*-butyl dicarbonate (0.42 mL, 3.2 mmol), and heated to reflux for 0.5 h. The reaction
 mixture was evaporated, and the residue purified by flash chromatography (SiO₂, 15–50% ethyl
 acetate/methylene chloride) to provide iodide **443** (0.72 g, 86% yield) as a colorless oil. Data for
443: MS (ESI) *m/z* 475 (M+H)⁺; ¹HNMR (300 MHz, CDCl₃): δ 8.85 (d, *J* = 4 Hz, 1H), 8.12 (d,
 20 *J* = 8 Hz, 1H), 7.98–7.82 (m, 1H), 7.72–7.66 (m, 1H), 7.61 (d, *J* = 8 Hz, 2H), 7.54–7.48 (m, 1H),
 7.16 (d, *J* = 5 Hz, 1H), 6.98–6.85 (m, 2H), 4.88–4.80 (m, 2H), 4.43–4.29 (m, 2H), 1.49–1.42 (m,
 9H).

Synthesis of azide 444

A solution of iodide **443** (0.22 g, 0.46 mmol) in dioxane (2.5 mL) was treated with triethylamine (0.19 mL, 1.4 mmol), pinacol borane (0.090 mL, 0.61 mmol), and Pd(dppf)Cl₂ (10 mg, 0.012 mmol) and heated to 80°C for 3 h. The reaction mixture was cooled to room temperature, diluted with ethanol (0.83 mL) and H₂O (0.83 mL), treated with potassium carbonate (0.19 g, 1.4 mmol), azide **253** (0.17 g, 0.46 mmol), and Pd(dppf)Cl₂ (10 mg, 0.012 mmol), and heated to 80°C for 3 h. The reaction mixture was cooled to room temperature, diluted with methylene chloride (50 mL), washed with saturated aqueous sodium bicarbonate (2 × 50 mL), dried (Na₂SO₄), and evaporated. Flash chromatography (SiO₂, 50–100% ethyl acetate/methylene chloride) provided azide **444** (0.18 g, 67% yield) as a yellow oil. Data for **444**: ¹HNMR (300 MHz, CD₃OD/CDCl₃): δ 8.76 (d, *J* = 5 Hz, 1H), 8.04–8.00 (m, 2H), 7.77–7.69 (m, 1H), 7.62–7.43 (m, 8H), 7.33–7.25 (m, 1H), 4.89–4.83 (m, 1H), 4.28 (s, 2H), 4.22–4.12 (m, 1H), 3.94 (s, 2H), 3.92–3.88 (m, 1H), 3.79–3.72 (m, 1H), 3.62–3.56 (m, 1H).

Synthesis of triazole **378**

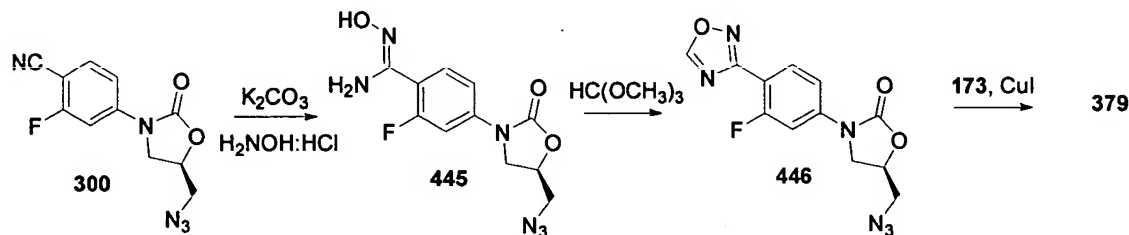
A solution of azide **444** (0.090 g, 0.15 mmol) in dichloromethane (4.0 mL) was treated with trifluoroacetic acid (4.0 mL) and stirred at 23°C for 1 h. The solvent was removed under reduced pressure, and the residue dissolved in chloroform (100 mL) and washed with 10% aqueous potassium carbonate (100 mL), dried (Na₂SO₄), and evaporated to provide 50 mg of deprotected amine as an orange solid.

A solution of this crude amine (0.0430 g, 0.089 mmol) and alkyne **173** (0.056 g, 0.071 mmol) in tetrahydrofuran (1.5 mL) was treated with *N,N*-diisopropylethylamine (0.015 mL, 0.089 mmol) and copper (I) iodide (2.0 mg, 0.0089 mmol) and stirred under argon at 23°C for 1 h. The reaction mixture was diluted with saturated aqueous ammonium hydroxide (10 mL) and extracted with dichloromethane (3 × 20 mL). The combined organic fractions were dried (Na₂SO₄) and evaporated, and the residue purified by preparative thin-layer chromatography (PTLC, SiO₂, ammonium hydroxide/methanol/ethyl acetate/dichloromethane 0.5:10:15:74.5) to provide **378** (44 mg, 48% yield) as a white powder. Data for **378**: MS (ESI) *m/z* 1270 (M+H)⁺; ¹HNMR (300 MHz, CDCl₃, partial): δ 8.89 (d, *J* = 5 Hz, 1H), 8.12 (d, *J* = 9 Hz, 1H), 8.06 (d, *J* = 8 Hz, 1H), 7.72–7.68 (m, 1H), 7.62 (s, 1H), 7.19–7.17 (m, 1H), 4.30 (s, 2H), 3.96 (s, 2H), 3.33 (s, 3H), 2.33 (s, 3H), 2.26 (s, 3H), 0.88–0.86 (m, 6H).

Example 47 – Synthesis of Triazole 379

Scheme 70 depicts the synthesis of triazole **379**. Azide **300** was converted to hydroxyamidine **445** which was subsequently cyclized with triethylorthoformate to oxadiazole azide **446**. The cycloaddition of **446** with alkyne **173** yielded triazole **379**.

Scheme 70



10 Synthesis of azide **446**

A solution of azide **300** (300 mg, 1.1 mmol) in ethanol (5.5 mL) was treated with potassium carbonate (152 mg, 1.1 mmol) and hydroxylamine hydrochloride (153 mg, 2.2 mmol) and refluxed for 3 h. The reaction was cooled to 23°C and the solvent was evaporated *in vacuo*. The crude hydroxyamidine was added to triethylorthoformate (5.5 mL) and the reaction was refluxed for 2 h, cooled to 23°C and stirred for 48 h, and then refluxed for 1 h. The reaction was then cooled to 23°C and diluted with ethyl acetate (20 mL). The organic layer was washed with 1 M hydrochloric acid (20 mL). Drying (Na_2SO_4) and evaporation provided oxadiazole azide **446** (80 mg, 0.26 mmol, 24% yield). Data for **446**: 1H NMR (300 MHz, $CDCl_3$): δ 8.80 (s, 1H), 8.12 (t, $J = 8$ Hz, 1H), 7.66 (dd, $J = 13, 2$ Hz, 1H), 7.43 (dd, $J = 9, 2$ Hz, 1H), 4.91-4.81 (m, 1H), 4.17-4.11 (m, 1H), 3.93 (dd, $J = 9, 6$ Hz, 1H), 3.77 (dd, $J = 4, 13$, 1H), 3.63 (dd, $J = 4, 13$, 1H).

Synthesis of triazole **379**

A solution of alkyne **173** (135 mg, 0.17 mmol) and azide **446** (65 mg, 0.21 mmol) in tetrahydrofuran (1.3 mL) was treated with diisopropylethylamine (0.037 mL, 0.21 mmol) and then degassed by application of vacuum and introduction of argon. Copper (I) iodide (4 mg, 0.021 mmol) was added, and the reaction was again degassed. The reaction was stirred under argon at 23°C for 1 h, and then purified by flash chromatography (SiO_2 , ammonium hydroxide/methanol/dichloromethane (0.05:1:12)) to provide **379** (153 mg, 0.14 mmol, 82%).

yield) as a white powder. Data for **379**: MS (ESI) m/z 1091.8 ($M+H$)⁺; ¹HNMR (300 MHz, CDCl₃, partial): δ 8.80 (s, 1H), 8.18-8.136 (m, 1H), 7.69 (s, 1H), 7.65 (dd, J = 13, 2, 1H), 7.37-7.33 (m, 1H), 4.82-4.80 (m, 1H), 4.67 (dd, J = 10, 2 Hz, 1H), 3.41 (s, 3H), 0.98-0.93 (m, 6H).

5 Example 48 – Synthesis of Triazole 380

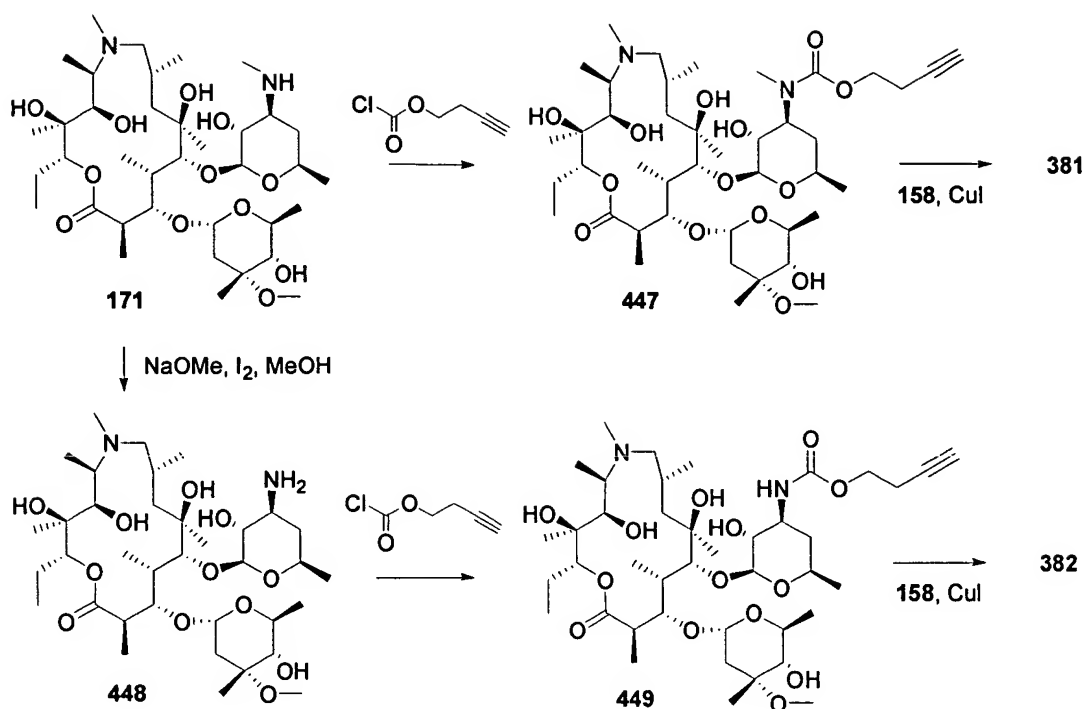
The required 3,5-difluoroaryl oxazolidinone azide was synthesized from 3,5-difluoroaniline using the chemistry reported in the literature (Brickner, S.J. *et al. J. Med. Chem.* 1996, 39, 673).

Alkyne **328** (70 mg, 86 μ mol), the above azide (33 mg, 129 μ mol), and CuI (2 mg, 8 μ mol) were reacted under the conditions described for the synthesis of triazole **228** to afford triazole **380** as a white solid (92.6 mg, 85 μ mol). Data for **380**: MS (ESI) m/z 543 ($M + 2H$)²⁺; ¹HNMR (300 MHz, CDCl₃, partial): δ 7.99 (bs, 1H), 7.42 (s, 1H), 7.00-6.92 (m, 2H), 6.51 (tt, J = 9, 2 Hz, 1H), 5.06-4.99 (m, 1H), 4.94 (d, J = 6 Hz, 1H), 4.66 (d, J = 5 Hz, 2H), 4.59 (dd, J = 9, 2 Hz, 1H), 4.38 (d, J = 7 Hz, 1H), 4.22 (dd, J = 6, 2 Hz, 1H), 4.10 (t, J = 8 Hz, 1H), 4.10-4.00 (m, 1H), 3.87-3.82 (m, 2H), 3.61-3.57 (m, 2H), 3.53-3.41 (m, 2H), 3.33 (s, 3H), 3.16 (dd, J = 10, 4 Hz, 1H), 2.96 (t, J = 10 Hz, 1H), 2.85-2.73 (m, 5H), 2.31 (s, 3H), 2.19 (s, 3H), 0.83 (d, J = 6 Hz, 3H), 0.81 (t, J = 7 Hz, 3H).

Example 49 – Synthesis of Triazoles 381 and 382

Scheme 71 depicts the synthesis of triazoles **381** and **382**. Amine **171** was converted to carbamate **447** prior to cycloaddition with azide **158** to afford triazole **381**. Amine **171** was demethylated to yield amine **448**, which was subsequently transformed to carbamate **449** and ultimately triazole **382**.

25 Scheme 71



Synthesis of carbamate **447**

To a stirred solution of **171** (0.72 g, 1.0 mmol) in CH₂Cl₂ (10 mL) and Hunig's base (1 mL), was added dropwise a CH₂Cl₂ solution of 4-butynyl chloroformate (135 mg, 1.01 mmol in 2 mL). The mixture was stirred at rt for 16 h, then diluted to 50 mL with CH₂Cl₂ and washed with sat. aq. NaHCO₃ (50 mL) and brine (25 mL). The organic fraction was dried over K₂CO₃, filtered and concentrated to give 0.9 g of a foam which was purified by silica gel chromatography (25mm x 6" column eluted with 50:1 CH₂Cl₂/2N NH₃ in MeOH) to afford carbamate **447** as a white solid (0.68 g, 0.83 mmol). Data for **447**: MS (ESI) *m/z* 815 (M + H)⁺; ¹HNMR (300 MHz, CDCl₃, partial): δ 8.72 (bs, 1H), 5.07 (d, *J* = 4 Hz, 1H), 4.95 (d, *J* = 7 Hz, 1H), 3.32 (s, 3H), 2.90 (s, 3H), 2.31 (s, 3H), 1.34-1.27 (m, 8H), 1.27-1.15 (m, 10H), 1.10-0.99 (m, 9H), 0.92-0.84 (m, 6H).

Synthesis of triazole **381**

Alkyne **447** (60 mg, 72 μmol), azide **158** (35 mg, 108 μmol), and CuI (2 mg, 8 μmol) were reacted under the conditions described for the synthesis of compound **228** to afford triazole **381** as a white solid (67 mg, 65 μmol). Data for **381**: MS (ESI) *m/z* 1137 (M + H)⁺; ¹HNMR (300 MHz, CDCl₃, partial): δ 8.9 (bs, 1H), 7.63 (s, 1H), 7.05-6.92 (m, 1H), 6.82 (t, *J* = 9 Hz,

1H), 5.10-4.90 (m, 2H), 4.80-4.00 (m, 7H), 3.90-3.81 (m, 3H), 3.70-3.58 (m, 2H), 3.41-3.25 (m, 3H) 3.20 (pent, $J = 6$, 1H), 3.10-2.96 (m, 4H), 2.92-2.38 (m 5H), 2.29 (s, 3H), 2.10-1.40 (m, 51H), 1.25-1.04 (m, 15H), 0.93 (d, $J = 8$, 3H), 0.94-0.83 (m, 6H).

5 Synthesis of amine 448

To a stirred solution of desmethyl azithromycin **171** (10.0 g, 13.6 mmol) in methanol (200 mL) was added sodium methoxide (1.33 g, 25 mmol). The mixture was cooled to 0°C prior to the addition of iodine (3.55 g, 14 mmol). The mixture was stirred at 0°C for 1.5 h, then warmed to rt over 1h. The reaction mixture was poured into ice water (1L) and the solution was adjusted to pH 12 by addition of KOH which led to the precipitation of a white solid. After sitting at 0°C for 1 h, the solid was filtered to give 7.2 g of crude product which was recrystallized from boiling methanol to give 3.8 g of product as white crystals. Data for **448**: MS (ESI) m/z 361.24 ($M + 2H$)²⁺; ¹HNMR (300 MHz, CDCl₃, partial): δ 8.48 (bs, 1H), 5.18 (bs, 1H), 4.95 (d, $J = 4$ Hz, 1H), 4.60 (dd, $J = 10$, 2 Hz, 1H), 4.30 (d, $J = 8$ Hz, 1H), 4.18 (dd, $J = 5$, 2 Hz, 1H), 4.06-3.96 (m, 1H), 3.60-3.48 (m, 3H), 3.27 (s, 3H) 2.28 (s, 3H).

Synthesis of carbamate 449

3'-N-bis-demethyl azithromycin **448** (180 mg, 0.25 mmol) was treated with 4-butyryl chlorofomate (35 mg, 0.25 mmol) under the same conditions described for the synthesis of **447** to afford carbamate **449** as a white solid (157 mg, 0.19 mmol). Data for **449**: MS (ESI) m/z 1123 ($M + H$)⁺; ¹HNMR (300 MHz, CDCl₃, partial): δ 8.18 (bs, 1H), 4.92 (d, $J = 4$ Hz, 1H), 4.78 (d, $J = 4$ Hz, 1H), 4.39 (d, $J = 6$ Hz, 1H), 4.15 (t, $J = 7$ Hz, 2H), 4.05-3.92 (m, 1H), 3.28 (s, 3H), 2.30 (s, 3H), 1.68 (d, $J = 8$ Hz, 1H), 1.51 (dd, $J = 8$, 3 Hz, 1H), 1.28-1.12 (m, 8H), 1.27-1.15 (m, 10H), 1.05 (d, $J = 7$ Hz, 3H), 1.00 (s, 3H), 0.91 (d, $J = 7$ Hz, 3H), 0.92-0.84 (m, 6H).

Synthesis of triazole 382

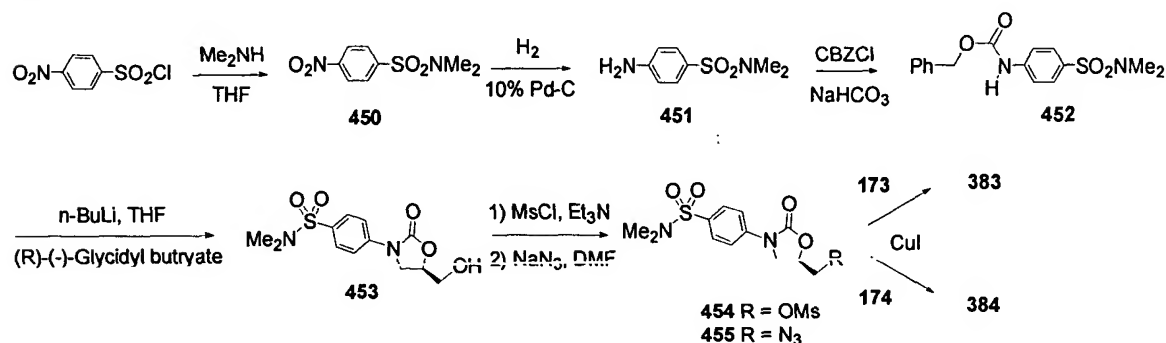
Alkyne **449** (40 mg, 49 μ mol), azide **158** (24 mg, 73 μ mol), and CuI (2 mg, 8 μ mol) were reacted under the conditions described for the synthesis of compound **228** to afford triazole **382** as a white solid (67 mg, 65 μ mol). Data for **382**: MS (ESI) m/z 1135 ($M + H$)⁺; ¹HNMR (300 MHz, CDCl₃, partial): δ 8.30 (bs, 1H), 7.54 (s, 1H), 7.11-7.02 (m, 2H), 6.82-6.70 (m, 2H), 5.41

(d, $J = 5$ Hz, 1H), 5.05-4.90 (m, 2H), 4.68 (d, $J = 4$ Hz, 1H), 4.59 (d, $J = 6$ Hz, 1H), 3.28 (s, 3H), 2.25 (s, 3H), 1.69 (d, $J = 8$ Hz, 1H), 1.31-1.01 (m, 15H), 0.95 (d, $J = 8$, 3H), 0.80 (t, $J = 8$, 3H).

Example 50 – Synthesis of Triazoles 383 and 384

Scheme 72 depicts the synthesis of triazoles **383** and **384**. 4-Nitrobenzenesulfonyl chloride was converted to sulfonamide **450** which was manipulated to carbamate **452** by standard chemistry. Oxazolidinone formation followed by azide formation gave **455**. The cycloaddition of **455** with alkynes **173** and **174** rendered triazoles **383** and **384** respectively.

Scheme 72



Synthesis of azide 455

4-Nitrobenzenesulfonyl chloride (2.22 g, 10 mmol) was added to a solution of dimethylamine (10 mL, 2.0 M in THF, 20 mmol) at 0°C. The reaction was stirred at 0°C for 1 h and then at room temperature for additional 1 h. The THF was removed under vacuum, more water was added, and the precipitate was collected by filtration and dried to afford **450** (2.20 g, 96% yield). Data for **450**: ^1H NMR (300 MHz, $\text{CDCl}_3\text{-CD}_3\text{OD}$): δ 8.33 (d, $J = 9$ Hz, 2H), 7.90 (d, $J = 9$ Hz, 2H), 2.70 (s, 6H).

To a solution of sulfonamide **450** (2.2 g, 9.6 mmol) in methanol (30 mL) was added 10% Pd-C (0.25 g) and the resulting mixture was stirred at room temperature for 6 h under 1 atm hydrogen atmosphere. The Pd-C was removed by filtration on celite. The filtered solution was evaporated to provide **451** (1.8 g, 94% yield) as a white solid. Data for **451**: ^1H NMR (300 MHz, CDCl_3): δ 7.43 (d, $J = 9$ Hz, 2H), 6.59 (d, $J = 9$ Hz, 2H), 2.53 (s, 6H).

Benzyl chloroformate (1.4 mL, 9.6 mmol) was added dropwise to a solution of aniline **451** (1.60 g, 8.0 mmol), and NaHCO_3 (2.70 g, 21 mmol) in a mixture of THF (5 mL) and water (3 mL) at 0°C. After stirring at 0°C for 2 h and room temperature for 4 h, the reaction mixture

was diluted with ethyl acetate (30 mL). The organic layer was washed with brine (3 x 50 mL), dried (MgSO₄) and concentrated to provide 2.35 g of white solid **452** in a yield of 93%. Data for **452**: ¹HNMR (300 MHz, CDCl₃): δ 7.79 (d, *J* = 9 Hz, 2H), 7.64 (d, *J* = 9 Hz, 2H), 7.50-7.45 (m, 5H), 7.02 (br s, 1H), 5.30 (s, 2H), 2.76 (s, 6H).

5 To a solution of CBZ-protected amine **452** (1.0 g, 3 mmol) in THF (20 mL) was added *n*-BuLi (3.3 mL, 1.6 M in hexane, 5.28 mmol) at -78°C and the mixture was stirred for 30 min. (*R*)-(-)-Glycidyl butyrate (0.53 mL, 3.75 mmol) was added, the reaction was stirred at -78°C for 3 h and was then warmed to room temperature and stirred overnight. The reaction was carefully quenched with saturated NH₄Cl and extracted with EtOAc. The organic phase was washed with
10 brine, dried (MgSO₄) and concentrated. The crude product was recrystallized from ethyl acetate to give alcohol **453** as a white crystalline solid (0.45 g, 50% yield). Data for **453**: MS (ESI) *m/z* 300.9 (M+H)⁺; ¹HNMR (300 MHz, CDCl₃): δ 7.83 (d, *J* = 9 Hz, 2H), 7.78 (d, *J* = 9 Hz, 2H), 4.86 (m, 1H), 4.19-4.07 (m, 3H), 3.85 (dd, *J* = 4, 13 Hz, 1H), 2.75 (s, 6H).

To a solution of alcohol **453** (200 mg, 0.67 mmol) and Et₃N (101 mg, 1.0 mmol) in
15 CH₂Cl₂ (5 mL) was added methanesulfonyl chloride (92 mg, 0.80 mmol) at 0°C. The mixture was stirred at room temperature for 30 min. The CH₂Cl₂ solution was washed with brine, dried (MgSO₄), concentrated and crystallized from EtOAc to afford mesylate **454** (238 mg, 94% yield). Data for **454**: MS (ESI) *m/z* 378.9 (M+H)⁺; ¹HNMR (300 MHz, CDCl₃): δ 7.80 (d, *J* = 9 Hz, 2H), 7.73 (d, *J* = 9 Hz, 2H), 4.98 (m, 1H), 4.54 (dd, *J* = 4, 12 Hz, 1H), 4.46 (dd, *J* = 4, 12
20 Hz, 1H), 4.23 (t, *J* = 9 Hz, 1H), 4.04 (dd, *J* = 6, 9 Hz, 1H), 3.11 (s, 3H), 2.70 (s, 6H).

A mixture of **454** (200 mg, 0.52 mmol) and sodium azide (137 mg, 2.11 mmol) in DMF (4 mL) was heated at 80°C for 3 h. The reaction mixture was diluted with EtOAc, washed with brine, dried (MgSO₄), concentrated and crystallized from EtOAc/MeOH to afford azide **455** (149 mg, 88% yield). Data for **455**: ¹HNMR (300 MHz, DMSO): δ 7.72 (d, *J* = 9 Hz, 2H), 7.67 (d, *J* = 9 Hz, 2H), 4.83 (m, 1H), 4.11 (t, *J* = 9 Hz, 1H), 3.77-3.58 (m, 3H), 2.58 (s, 6H).
25

Synthesis of triazole **383**

A mixture of alkyne **173** (118 mg, 0.15 mmol), azide **455** (54 mg, 0.165 mmol) and copper (I) iodide (28.5 mg, 0.15 mmol) in THF (5 mL) was repeatedly degassed and flushed with
30 argon. Hunig's base (0.26 mL) was introduced and the mixture stirred at room temperature for 12 h. The reaction mixture was poured into saturated NH₄Cl (30 mL) and stirred for 15 minutes.

The mixture was extracted with CH₂Cl₂, washed with brine, dried over MgSO₄ and concentrated. Chromatography on silica gel (25:1:0.05 CH₂Cl₂/MeOH/NH₃-H₂O as eluant) provided **383** (145 mg, 87% yield) as a white foam. Data for **383**: MS (ESI) *m/z* 1112.7 (M+H)⁺, 557.1 (100%); ¹HNMR (300 MHz, CDCl₃, partial): δ 7.70 (d, *J* = 9 Hz, 2H), 7.61 (s, 1H), 7.60 (d, *J* = 9 Hz, 2H), 3.32 (s, 3H), 2.66 (s, 6H), 2.28 (s, 3H), 2.26 (s, 3H), 0.87 (t, *J* = 8 Hz, 3H).

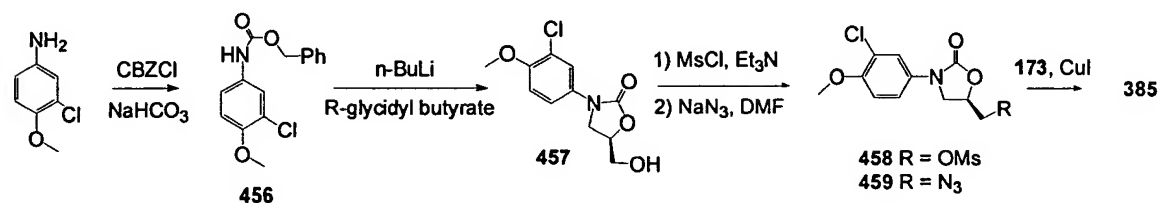
Synthesis of triazole **384**

A mixture of alkyne **174** (120 mg, 0.15 mmol), azide **445** (54 mg, 0.165 mmol) and copper (I) iodide (28.5 mg, 0.15 mmol) in THF (5 mL) was repeatedly degassed and flushed with argon. Hunig's base (0.26 mL) was introduced and the mixture stirred at room temperature for 12 h. The reaction mixture was poured into saturated NH₄Cl (30 mL) and stirred for 15 minutes. The mixture was extracted with CH₂Cl₂, washed with brine, dried over MgSO₄ and concentrated. Chromatography on silica gel (25:1:0.05 CH₂Cl₂/MeOH/NH₃-H₂O as eluant) provided **384** (150 mg, 89% yield) as a white foam. Data for **384**: MS (ESI) *m/z* 1126.7 (M+H)⁺, 564.1 (100%); ¹HNMR (300 MHz, CDCl₃, partial): δ 7.74 (d, *J* = 9 Hz, 2H), 7.60 (d, *J* = 9 Hz, 2H), 7.52 (s, 1H), 3.33 (s, 3H), 2.68 (s, 6H), 2.32 (s, 3H), 2.23 (s, 3H), 0.89 (t, *J* = 8 Hz, 3H).

Example 51 – Synthesis of Triazoles **385-389**

Scheme 73 depicts the synthesis of triazole **385**. 3-Chloro-4-methoxyaniline was converted to carbamate **456** which was subsequently parlayed to azide **459**. The cycloaddition of **459** with alkyne **173** afforded triazole **385**. The same chemistry depicted in Scheme 73 was used to synthesize triazoles **386-389** from the appropriate anilines.

Scheme 73



Synthesis of azide 459

Sodium bicarbonate (2.69 g, 25.4 mmol) was dissolved in water (22 mL) and (45 mL) acetone. To this solution p-anisidine (2.0 g, 12.7 mmol) was added. The mixture was cooled to 0°C, and benzyl chloroformate (1.81 mL, 12.70 mmol) was added. The mixture was stirred 5 min at 0°C, the cold bath removed, and then stirring was continued at room temperature overnight (~16 hours). The mixture was evaporated, and partitioned with a 1:1 mixture of ethyl acetate and water. The organic layer was washed with water, and then brine. The organic layer was dried with Na₂SO₄, and evaporated to yield carbamate **456** (3.20 g, 86% yield) of suitable purity for use in subsequent reactions. Data for **456**: ¹HNMR (300 MHz, CDCl₃): δ 7.50 (s, 1H), 7.30 (m, 5H), 7.10 (d, *J* = 5 Hz, 1H), 6.80 (d, *J* = 8 Hz, 1H), 5.15 (s, 2H), 3.84 (s, 3H).

Carbamate **456** (1.0 g, 3.43 mmol) was dissolved in 50 mL tetrahydrofuran, and the solution cooled to -78°C. n-Butyllithium (2.5 M in hexane, 2.1 mL, 3.43 mmol) was added slowly, and the mixture allowed to stir for 45 min at -78°C. R-Glycidyl butyrate (0.5 mL, 3.5 mmol) was added, and the mixture was stirred for 1 h at -78°C. The bath was removed and the reaction allowed to stir overnight at room temperature. The reaction was quenched with 10 mL saturated ammonium chloride solution, and partitioned with ethyl acetate and water. The aqueous layer was extracted thrice with ethyl acetate, and the combined organic layer was washed with brine, dried (Na₂SO₄), and evaporated to yield alcohol **457** (0.5 g, 63% yield) of suitable purity for use in subsequent reactions. Data for **457**: ¹HNMR (300 MHz, CDCl₃): δ 7.49 (s, 1H), 7.35 (m, 1H), 6.84 (d, *J* = 5 Hz, 1H), 4.71 (m, 1H), 3.95 (m, 2H).

Alcohol **457** (0.5 g, 1.94 mmol) was dissolved in 5 mL methylene chloride, and the mixture cooled to 0°C. Triethylamine (0.54 mL, 3.88 mmol) was added, followed by methanesulfonyl chloride (0.2 mL, 2.72 mmol). The mixture was allowed to warm to room temperature and stirred for 1 hr. Methylene chloride (10 mL) was added, and the mixture washed twice with 1N HCl, then twice with 10% aqueous sodium carbonate, and then brine. The organic phase was dried (Na₂SO₄), and evaporated to yield mesylate **458** (0.60 g, 92% yield).

A solution of mesylate **458** (0.60 g, 1.79 mmol) in dimethylformamide (5 mL) was treated with sodium azide (0.46 g, 7.15 mmol) and the mixture heated to 80°C for 5 h. The reaction mixture was cooled to room temperature, diluted with ethyl acetate (50 mL), and washed with brine (2 x 50 mL). Drying (Na₂SO₄), and evaporation provided azide **459** (0.45 g, 90% yield) as a yellow solid of suitable purity for use in subsequent reactions. Data for **459**:

¹H-NMR (300 MHz, CDCl₃): δ 7.50 (s, 1H), 7.35 (dd, *J* = 2, 5 Hz, 1H), 6.87 (d, *J* = 9 Hz, 1H), 4.75 (m, 1H), 4.0 (t, *J* = 9 Hz, 1H), 3.75 (dd, *J* = 9, 13 Hz, 1H), 3.52 (dd, *J* = 5, 13 Hz, 1H).

Synthesis of triazole 385

5 A solution of but-3-ynyl-methyl-amino azithromycin **173** (100 mg, 0.127 mmol) in tetrahydrofuran (5 mL) was treated with azide **459** (53.0 mg, 0.19 mmol), *N,N*-diisopropylethylamine (0.026 mL, 0.15 mmol) and copper (I) iodide (0.018 g, 0.095 mmol), and the mixture was stirred under argon at room temperature for 16 h. The reaction mixture was diluted with ethyl acetate (50 mL), and washed with brine (2 x 50 mL). The organic phase was
10 dried and evaporated. The residue was purified by preparative thin layer chromatography (using 80% CH₂Cl₂, 20% MeOH, 1 % NH₄OH as eluant) to provide triazole **385** (64 mg, 50% yield) as a white solid. Data for **385**: ¹H-NMR (300 MHz, CDCl₃, partial): δ 7.60 (s, 1H), 7.40 (s, 1H), 7.10 (s, 1H), 6.80 (d, *J* = 3 Hz, 1H), 4.95 (m, 1H), 4.60 (m, 1H), 4.40 (m, 1H), 4.20 (m, 1H), 4.0 (m, 1H), 3.50 (m, 1H), 3.20 (s, 2H).

15

Synthesis of triazoles 386-389

 The azides required for the synthesis of triazoles **386-389** were synthesized from the appropriate amines using the chemistry reported in the literature (Brickner, S.J. *et al. J. Med. Chem.* **1996**, 39, 673). The azides were treated with alkyne **173**, using the conditions reported
20 above for the synthesis of triazole **385**, to afford the targets **386-389**.

 Data for **386**: ¹H-NMR (300 MHz, CDCl₃, partial): δ 7.50 (s, 1H), 5.0 (s, 1H), 4.80 (m, 1H), 4.60 (m, 2H), 4.47 (m, 2H), 3.98-4.20 (m, 5H), 3.60 (m, 2H), 3.25 (d, *J* = 6 Hz, 3H), 2.20 (m, 3H).

 Data for **387**: ¹H-NMR (300 MHz, CDCl₃, partial): δ 7.46 (s, 1H), 7.37 (d, *J* = 2 Hz, 2H), 7.20 (m, 2H), 5.10 (s, 1H), 5.00 (m, 2H), 4.70 (m, 2H), 4.45 (d, *J* = 3 Hz, 1H), 4.20 (s, 1H), 4.15 (m, 3H).

 Data for **388**: ¹H-NMR (300 MHz, CDCl₃, partial): δ 9.0 (s, 1H), 7.50 (m, 4H), 5.0 (m, 2H), 4.70 (m, 3H), 4.30 (d, *J* = 2 Hz, 1H), 4.20 (s, 1H), 4.10 (m, 1H), 4.0 (m, 1H), 3.98 (m, 1H), 3.60 (m, 2H), 3.20 (m, 3H), 2.98 (t, *J* = 7 Hz, 1H).

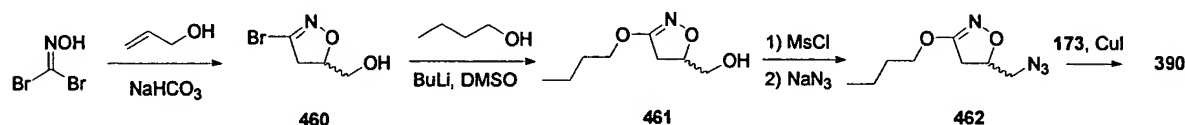
30 Data for **389**: ¹H-NMR (300 MHz, CDCl₃, partial): δ 9.20 (s, 1H), 7.50 (s, 1H), 7.30 (m, 2H), 6.80 (m, 1H), 5.10 (d, *J* = 5 Hz, 1H), 4.98 (m, 1H), 4.80 (d, *J* = 3 Hz, 1H), 4.60 (m, 2H),

4.30 (d, $J = 2$ Hz, 1H), 4.20 (s, 1H), 4.0 (m, 2H), 3.80 (s, 3H), 3.60 (m, 2H), 3.27 (s, 3H), 3.11 (app t, $J = 7$ Hz, 1H).

Example 52 – Synthesis of Triazole 390

Scheme 74 depicts the synthesis of triazole **390**. The cycloaddition of dibromo hydroxyformimine and allyl alcohol provided bromo isoxazoline **460** which was then converted into alcohol **461**. The alcohol of **461** was transformed to the azide **462** which underwent cycloaddition to alkyne **173** to afford triazole **390**.

Scheme 74



Synthesis of isoxazoline **460**

A mixture of dibromo hydroxyformimine (1 g, 4.93 mmol), allyl alcohol (1.68 mL, 24.7 mmol), NaHCO_3 (1.58 g, 18.7 mmol) in 1.5 mL water and 18 mL ethyl acetate was stirred overnight at room temperature. The mixture was then poured into 20 mL of water and extracted with ethyl acetate (2 x 20 mL). The combined organic extract was washed with brine (10 mL), dried (Na_2SO_4) and evaporated, yielding **460** (828 mg, 93%). Data for **460**: ^1H NMR (300 MHz, CDCl_3): δ 4.80-4.65 (m, 1H), 3.85-3.74 (m, 1H), 3.61-3.52 (m, 1H), 3.22-3.05 (m, 2H), 1.95-1.75 (br s, 1H).

Synthesis of alcohol **461**

To a solution of 1-butanol (5.1 mL, 55.6 mmol) in 25 mL DMSO was added a 2.5 M $n\text{-BuLi}$ solution in hexanes (3.9 mL, 9.72 mmol). The mixture was stirred at room temperature for 20 min, then a solution of **460** (500 mg, 2.78 mmol) in 2 mL DMSO was added. The mixture was stirred at room temperature for 3 h, poured into 50 mL water/ice and extracted with ethyl acetate (3 x 40 mL). The combined organic extract was washed with water (4 x 20 mL), brine (20 mL), dried (Na_2SO_4) and evaporated. The residue was purified by flash-chromatography (eluant: hexanes-ethyl acetate 2:1) yielding **461** (165 mg, 34%). Data for **461**: ^1H NMR (300 MHz, CDCl_3): δ 4.69-4.60 (m, 1H), 4.09-4.00 (m, 2H), 3.78-3.69 (m, 1H), 3.59-3.51 (m, 1H), 2.99-2.78 (m, 2H), 1.68-1.55 (m, 2H), 1.40-1.25 (m, 2H), 0.90-0.82 (m, 3H).

Synthesis of azide 462

To a solution of **461** (165 mg, 0.95 mmol) in 3 mL dichloromethane was added Et₃N (0.24 mL, 1.72 mmol) followed by MsCl (0.089 mL, 1.14 mmol) at 0°C. The mixture was stirred at 0°C for 1 h, poured into 10 mL water/ice and extracted with dichloromethane (2 x 10 mL). The combined organic extract was washed with water (2 x 10 mL), brine (10 mL), dried (Na₂SO₄) and evaporated. The residue was dissolved in 3 mL DMF, NaN₃ (124 mg, 1.91 mmol) was added, and the mixture was stirred at 80°C for 2 h. The mixture was poured into 10 mL water/ice and extracted with ethyl acetate (2 x 10 mL). The combined organic extract was washed with water (2 x 10 mL), brine (10 mL), dried (Na₂SO₄) and evaporated. The residue was purified by flash-chromatography (eluant: hexanes-ethyl acetate 3:1) yielding **462** (155 mg, 82%). Data for **462**: ¹HNMR (300 MHz, CDCl₃): δ 4.98-4.85 (m, 1H), 4.31-4.25 (m, 2H), 3.72-3.51 (m, 2H), 3.25-3.15 (m, 1H), 3.05-2.91 (m, 1H), 1.92-1.81 (m, 2H), 1.62-1.50 (m, 2H), 1.15-1.05 (m, 3H).

Synthesis of triazole 390

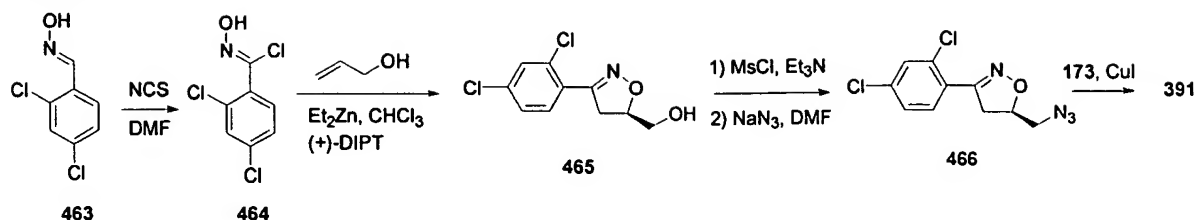
To a solution of alkyne **173** (150 mg, 0.191 mmol) in 6 mL acetonitrile was added **462** (37.8 mg, 0.191 mmol), 2,6-lutidine (0.025 mL, 0.209 mmol) and CuI (18.2 mg, 0.095 mmol). The mixture was stirred over night at room temperature, then poured into 10 mL 5% aqueous NH₃/ice and extracted with CH₂Cl₂ / isopropanol 95:5 (3 x 20 mL). The combined organic extract was washed with brine (10 mL), dried (Na₂SO₄) and evaporated. The residue was purified by flash-chromatography (eluant: ethyl acetate-MeOH 5:1) yielding **390** (131 mg, 70%). Data for **390**: MS (ESI) *m/z* 985 (M+H)⁺; ¹HNMR (300 MHz, CDCl₃, partial): δ 8.25-8.05 (br s, 1H) 7.66 (s, 1H), 5.12-4.90 (m, 3H).

Example 53 – Synthesis of Triazoles 391-393

Scheme 75 depicts the synthesis of triazole **391**. The oxime of 2,4-dichlorobenzaldehyde was converted to hydroxyiminoyl chloride **464** prior to cycloaddition to alcohol **465**. Conversion of alcohol **465** to azide **466** and final cycloaddition to alkyne **173** afforded triazole **391**.

Triazoles **392** and **393** were synthesized in the same manner as compound **391**.

Scheme 75



Synthesis of oxime 463

To a suspension of 2,4-dichlorobenzaldehyde (7.73 g, 44.2 mmol) in 100 mL 95% aqueous EtOH was added HCl·H₂NOH (3.69 g, 53.0 mmol) followed by a solution of NaOH (2.3 g, 57.4 mmol) in 4 mL of water at 0°C. The suspension was stirred at room temperature overnight, poured into 300 mL ice/water and extracted with ethyl acetate (2 x 100 mL). The combined organic extract was washed with water (2 x 80 mL), brine (80 mL), dried (Na₂SO₄) and evaporated yielding **463** (8.2 g, 97%). Data for **463**: ¹HNMR (300 MHz, CDCl₃): δ 8.52 (s, 1H), 7.80-8.75 (m, 1H), 7.43-7.40 (m, 1H), 7.29-7.20 (m, 1H).

Synthesis of hydroxyiminoyl chloride 464

To a solution of **463** (7.0 g, 36.8 mmol) in 30 mL DMF was added in portions N-chlorosuccinimide (5.4 g, 40.5 mmol) at 20-30°C. The mixture was stirred at room temperature for 1h, then poured into 200 mL ice/water and extracted with ethyl acetate (2 x 100 mL). The combined organic extract was washed with water (3 x 80 mL), brine (80 mL), dried (Na₂SO₄) and evaporated yielding **464** (7.1 g, 86%). Data for **464**: ¹HNMR (300 MHz, CDCl₃): δ 8.64 (s, 1H), 7.38-7.15 (m, 3H).

Synthesis of alcohol 465

To a solution of allyl alcohol (1.33 mL, 19.6 mmol) in 58 mL CHCl₃ was added a 1M diethylzinc solution in hexanes (23.2 mL, 23.2 mmol) at -5 to 0°C. After stirring for 10 min, (+)-diisopropyl tartrate (0.75 mL, 3.56 mmol) was added and the solution was stirred for 1 h at 0°C. The milky solution was cooled to -20°C and 14 mL CHCl₃ and dioxane (1.97 mL, 23.2 mmol) was added. Then **464** (4.00 g, 17.8 mmol) was added in portions at -20 to -15°C. The solution was stirred for 4 h at -10°C, then poured into 200 mL 1M citric acid/ice and extracted with CHCl₃ (3 x 100 mL). The combined organic extract was washed with brine (80 mL), dried (Na₂SO₄) and evaporated. The residue was purified by flash-chromatography (eluant: ethyl

acetate-hexanes 2:3), yielding crude **465**, which was recrystallized from 1-chlorobutane, yielding pure **465** (2.6 g, 60%). Data for **465**: ^1H NMR (300 MHz, CDCl_3): δ 7.76 (d, J = 5 Hz, 1H), 7.61 (s, 1H), 7.49-7.42 (m, 1H), 5.10-5.01 (m, 1H), 4.07 (dd, J = 3, 12 Hz, 1H), 4.03 (dd, J = 3, 12 Hz, 1H), 3.73-3.52 (m, 2H), 2.18 (br s, 1H).

5

Synthesis of azide **466**

To a solution of **465** (1.0 g, 4.1 mmol) in 20 mL dichloromethane was added Et_3N (1.0 mL, 7.3 mmol) followed by MsCl (0.37 mL, 4.9 mmol) at 0°C . The mixture was stirred at 0°C for 1 h, poured into 50 mL water/ice and extracted with dichloromethane (2 x 40 mL). The combined organic extract was washed with water (2 x 20 mL), brine (20 mL), dried (Na_2SO_4) and evaporated. The residue was dissolved in 17 mL DMF, NaN_3 (0.53 g, 8.1 mmol) was added, and the mixture was stirred at 80°C for 2 h. The mixture was poured into 50 mL water/ice and extracted with ethyl acetate (2 x 50 mL). The combined organic extract was washed with water (3 x 20 mL), brine (20 mL), dried (Na_2SO_4) and evaporated. The residue was purified by flash-chromatography (eluant: hexanes-ethyl acetate 2:3) yielding **466** (1.1 g, 98%). Data for **466**: ^1H NMR (300 MHz, CDCl_3): δ 7.65 (d, J = 8 Hz, 1H), 7.61 (d, J = 1 Hz, 1H), 7.23-7.17 (m, 1H), 4.90-4.82 (m, 1H), 3.61-3.21 (m, 4H).

Synthesis of triazole **391**

To a solution of alkyne **173** (150 mg, 0.191 mmol) in 6 mL acetonitrile was added azide **466** (52 mg, 0.191 mmol), 2,6-lutidine (0.025 mL, 0.209 mmol) and CuI (18.2 mg, 0.095 mmol). The mixture was stirred overnight at room temperature, poured into 10 mL 5% aqueous NH_3 /ice and extracted with CH_2Cl_2 /isopropanol 95:5 (3 x 20 mL). The combined organic extract was washed with brine (10 mL), dried (Na_2SO_4) and evaporated. The residue was purified by flash-chromatography (eluant: ethyl acetate-MeOH 5:1) yielding **391** (157 mg, 78%). Data for **391**: MS (ESI) m/z 1057 ($\text{M}+\text{H}$) $^+$; ^1H NMR (300 MHz, CDCl_3 , partial): δ 8.30-8.10 (br s, 1H), 7.52 (s, 1H), 7.39-7.20 (m, 3H), 5.15-5.02 (m, 1H).

Synthesis of triazole **392**

To a suspension of 4-chloro-3-fluorobenzaldehyde (5.00 g, 31.5 mmol) in 90 mL 95% aqueous EtOH was added $\text{HCl}\cdot\text{H}_2\text{NOH}$ (2.63 g, 37.8 mmol) followed by a solution of NaOH

(1.90 g, 47.3 mmol) in 3 mL of water at 0°C. The suspension was stirred at room temperature for 3 h, then poured into 200 mL ice/water and extracted with ethyl acetate (2 x 100 mL). The combined organic extract was washed with water (2 x 80 mL), brine (80 mL), dried (Na₂SO₄) and evaporated. The residue was dissolved in 25 mL DMF and N-chlorosuccinimide (4.23 g, 34.7 mmol) was added in portions at 30-40°C. The mixture was stirred at room temperature for 1 h, then poured into 200 mL ice/water and extracted with ethyl acetate (2 x 100 mL). The combined organic extract was washed with water (3 x 80 mL), brine (80 mL), dried (Na₂SO₄) and evaporated yielding the hydroxyiminoyl chloride (3.71 g., 62%). Data: ¹HNMR (300 MHz, CDCl₃): δ 8.15 (s, 1H), 7.60-7.51 (m, 2H), 7.41-7.32 (m, 1H).

To a solution of allyl alcohol (1.16 mL, 17.0 mmol) in 50 mL CHCl₃ at -5 to 0°C was added a 1M diethylzinc solution in hexanes (20.1 mL, 20.1 mmol). After stirring for 10 min, (+)-diisopropyl tartrate (0.65 mL, 3.09 mmol) was added and the solution was stirred for 1 h at 0°C. The milky solution was cooled to -20°C and 12 mL CHCl₃ and dioxane (1.70 mL, 20.1 mmol) was added. Then the above hydroxyiminoyl chloride (3.21 g, 15.4 mmol) was added in portions at -20 to -15°C. The solution was stirred for 3 h at -15°C, then poured into 200 mL 1M citric acid/ice and extracted with CHCl₃ (3 x 100 mL). The combined organic extract was washed with brine (80 mL), dried (Na₂SO₄) and evaporated. The residue was purified by flash-chromatography (eluant: ethyl acetate-hexanes 1:2 and 1:2), yielding crude material which was recrystallized twice from 1-chlorobutane, yielding the expected isoxazoline alcohol (1.5 g, 42%). Data: ¹HNMR (300 MHz, CDCl₃): δ 7.48-7.21 (m, 3H), 4.82-4.74 (m, 1H), 3.82-3.76 (m, 1H), 3.58-3.53 (m, 1H), 3.27-3.09 (m, 2H).

To a solution of the above alcohol (1.0 g, 4.4 mmol) in 20 mL dichloromethane was added Et₃N (1.1 mL, 7.8 mmol) followed by MsCl (0.41 mL, 5.2 mmol) at 0°C. The mixture was stirred at 0°C for 1h, then poured into 50 mL water/ice and extracted with dichloromethane (2 x 40 mL). The combined organic extract was washed with water (2 x 20 mL), brine (20 mL), dried (Na₂SO₄) and evaporated. The residue was dissolved in 15 mL DMF, NaN₃ (0.57 g, 8.7 mmol) was added and the mixture was stirred at 80°C for 2 h. The mixture was poured into 50 mL water/ice and extracted with ethyl acetate (2 x 50 mL). The combined organic extract was washed with water (3 x 20 mL), brine (20 mL), dried (Na₂SO₄) and evaporated. The residue was purified by flash-chromatography (eluant: hexanes-ethyl acetate 2:3) yielding the expected azide

(1.1 g, 95%). Data: ¹HNMR (300 MHz, CDCl₃): δ 7.43-7.29 (m, 3H), 4.93-4.84 (m, 1H), 3.54-3.27 (m, 3H), 3.18-3.30 (m, 1H).

To a solution of alkyne **173** (150 mg, 0.191 mmol) in 6 mL acetonitrile was added the above azide (49.5 mg, 0.191 mmol), 2,6-lutidine (0.0245 mL, 0.209 mmol) and CuI (18.2 mg, 0.095 mmol). The mixture was stirred overnight at room temperature, poured into 10 mL 5% aqueous NH₃/ice and extracted with CH₂Cl₂/isopropanol 95:5 (3 x 20 mL). The combined organic extract was washed with brine (10 mL), dried (Na₂SO₄) and evaporated. The residue was purified by flash-chromatography (eluant: ethyl acetate-MeOH 5:1) yielding **392** (138 mg, 70%). Data for **392**: MS (ESI) *m/z* 1042 (M+H)⁺; ¹HNMR (300 MHz, CDCl₃, partial): δ 8.45-8.32 (br s, 1H), 7.28-7.19 (m, 2H), 7.13-7.10 (m, 1H), 5.05-4.82 (m, 2H).

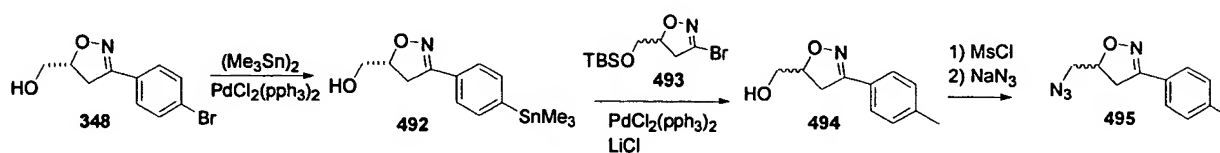
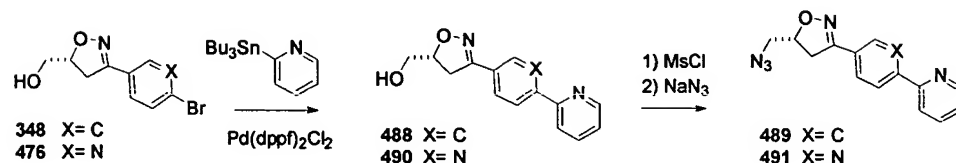
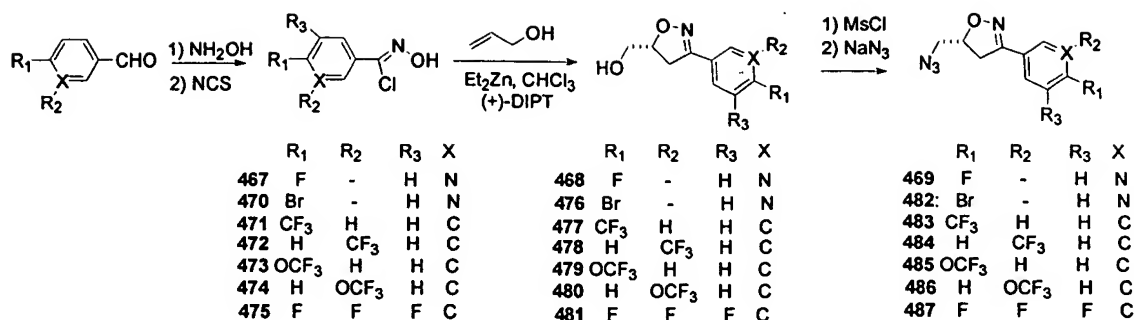
Synthesis of triazole **393**

To a solution of alkyne **173** (150 mg, 0.191 mmol) in 6 mL acetonitrile was added azide **342** (45.4 mg, 0.191 mmol), 2,6-lutidine (0.025 mL, 0.209 mmol) and CuI (18.2 mg, 0.095 mmol). The mixture was stirred overnight at room temperature, then poured into 10 mL 5% aqueous NH₃/ice and extracted with CH₂Cl₂/isopropanol 95:5 (3 x 20 mL). The combined organic extract was washed with brine (10 mL), dried (Na₂SO₄) and evaporated. The residue was purified by flash-chromatography (eluant: ethyl acetate-MeOH 5:1) yielding **393** (118 mg, 60%). Data for **393**: MS (ESI) *m/z* 1025 (M+H)⁺; ¹HNMR (300 MHz, CDCl₃, partial): δ 8.00 (br s, 1H), 7.52 (m, 3 H), 5.11-4.95 (m, 1H), 4.95-4.82 (m, 2H).

Example 54 – Synthesis of Triazoles **394-403**

Scheme 76 depicts the synthesis of azides **469**, **482-487**, **489**, **491**, and **495** required for the synthesis of triazoles **394-403**. The azides were then treated with alkyne **173** to afford the final targets.

Scheme 76



Synthesis of hydroxyiminoyl chloride 467

To a solution of 3-formyl-6-fluoropyridine (1.77 g, 9.36 mmol) in EtOH (10 mL) at 0°C was added water (5 mL), then hydroxylamine (1.00 g, 14.0 mmol), followed by the addition of NaOH (2.20 mL, 50%w/w). The mixture was stirred at 0°C for 15 min. The EtOH was evaporated, then EtOAc (50 mL) was added. HCl (1 M) was used to adjust pH to 6. The aqueous phase was extracted with EtOAc (30 mL x 2), and the organic extracts were dried by Na₂SO₄. The concentrated residue (1.50 g) was used in the next step without further purification.

To a solution of the crude intermediate above (1.50 g, in DMF (20 mL) at room temperature was added N-chlorosuccinimide (1.80 g, 13.1 mmol) in two portions. The mixture was stirred at 45-50°C for 1 h, then brine (50 mL) and saturated aqueous Na₂CO₃ (3 mL) was added. The mixture was extracted with EtOAc/Hexane (200 mL, 1/1). The organic layer was washed by brine (200 mL), dried by MgSO₄, to give hydroxyiminoyl chloride **467** (1.45 g, 60% yield). Data for **467**: ¹H NMR (300 MHz, CDCl₃): δ 8.72 (d, *J* = 3 Hz, 1H), 8.45 (s, 1H), 8.30-8.20 (m, 1H), 7.00 (dd, *J* = 9, 3 Hz, 1H).

Synthesis of hydroxyiminoyl chlorides 470-475

These hydroxyiminoyl chlorides were synthesized from the appropriate aryl aldehyde using the above procedure for the synthesis of 467.

Data for 470: ^1H NMR (300 MHz, CDCl_3): δ 9.27 (s, 1H), 8.86 (d, $J = 3$ Hz, 1H), 7.90-7.70 (m, 1H), 7.54 (d, $J = 8$ Hz, 1H).

Data for 471: ^1H NMR (300 MHz, CDCl_3): δ 8.16 (s, 1H), 7.94 (d, $J = 8$ Hz, 2H), 7.67 (d, $J = 8$ Hz, 2H).

Data for 472: ^1H NMR (300 MHz, CDCl_3): δ 8.53 (s, 1H), 8.02 (d, $J = 8$ Hz, 1H), 7.70 (d, $J = 8$ Hz, 1H), 7.56 (d, $J = 8$ Hz, 1H).

Data for 475: ^1H NMR (300 MHz, CDCl_3): δ 8.08 (s, 1H), 7.58-7.22 (m, 1H).

Synthesis of alcohol 468

To a solution of allyl alcohol (661 μL , 9.62 mmol) in CHCl_3 (30 mL) at 0°C was added diethylzinc (12.03 mL, 12.03 mmol). After the mixture was stirred at 0°C for 15 min, (+)-diisopropyl tartrate (855 μL , 4.01 mmol) in CHCl_3 (5.0 mL) was added. The mixture was stirred at 0°C for 1 h, then hydroxyiminoyl chloride 467 (1.40 g, 8.02 mmol) in CHCl_3 (10.0 mL) was added dropwise over 10 min. The mixture was stirred at 0°C for 2 h, then sat. aqueous NH_4Cl (20 mL) and citric acid (6 mL, 1 M) was added. The mixture was extracted with CH_2Cl_2 (50 mL x 4), and the organic extracts were dried by Na_2SO_4 . The residue was purified by flash-chromatography (eluant: 2.5/100 MeOH/ CH_2Cl_2), to provide 468 (1.40 g, 89% yield; >95% ee).
Data for 468: ^1H NMR (300 MHz, CDCl_3): δ 8.39 (d, $J = 3$ Hz, 1H), 8.25-8.15 (m, 1H), 7.00 (dd, $J = 9, 3$ Hz, 1H), 4.98-4.88 (m, 1H), 3.94 (dd, $J = 12, 3$ Hz, 1H), 3.72 (dd, $J = 12, 4$ Hz, 1H), 3.69-3.25 (m, 2H).

Synthesis of alcohols 476-481

These alcohols were synthesized from the appropriate hydroxyiminoyl chlorides using the above procedure for the synthesis of 468.

Data for 476: ^1H NMR (300 MHz, CDCl_3): δ 8.54 (d, $J = 3$ Hz, 1H), 7.92 (dd, $J = 11, 3$ Hz, 1H), 7.55 (d, $J = 8$ Hz, 1H), 4.99-4.90 (m, 1H), 3.94 (dd, $J = 12, 3$ Hz, 1H), 3.71 (dd, $J = 12, 4$ Hz, 1H), 3.47-3.93 (m, 2H).

Data for **477**: ^1H NMR (300 MHz, CDCl_3): δ 7.77 (d, $J = 8$ Hz, 2H), 7.65 (d, $J = 8$ Hz, 2H), 4.93 (dddd, $J = 13, 8, 4, 3$ Hz, 1H), 3.93 (dd, $J = 13, 3$ Hz, 1H), 3.70 (dd, $J = 13, 4$ Hz, 1H), 3.40 (dd, $J = 17, 11$ Hz, 1H), 3.32 (dd, $J = 17, 8$ Hz, 1H).

Data for **478**: ^1H NMR (300 MHz, CDCl_3): δ 7.87 (d, $J = 8$ Hz, 1H), 7.84 (d, $J = 8$ Hz, 1H), 7.65 (d, $J = 8$ Hz, 1H), 7.52 (d, $J = 8$ Hz, 1H), 4.93 (dddd, $J = 13, 8, 3, 3$ Hz, 1H), 3.92 (dd, $J = 13, 3$ Hz, 1H), 3.70 (dd, $J = 13, 4$ Hz, 1H), 3.43 (dd, $J = 11, 7$ Hz, 1H), 3.33 (dd, $J = 11, 8$ Hz, 1H).

Data for **479**: ^1H NMR (300 MHz, CDCl_3): δ 7.76 (d, $J = 7$ Hz, 2H), 7.31 (d, $J = 7$ Hz, 2H), 4.96 (dddd, $J = 13, 8, 4, 3$ Hz, 1H), 3.96 (dd, $J = 12, 3$ Hz, 1H), 3.75 (dd, $J = 12, 5$ Hz), 3.44 (dd, $J = 17, 10$ Hz, 1H), 3.34 (dd, $J = 17, 8$ Hz, 1H).

Data for **480**: ^1H NMR (300 MHz, CDCl_3): δ 7.58 (d, $J = 8$ Hz, 1H), 7.54 (s, 1H), 7.44 (d, $J = 8$ Hz, 1H), 7.31-7.24 (m, 1H), 4.92 (dddd, $J = 12, 8, 4, 3$ Hz, 1H), 3.94 (dd, $J = 5, 3$ Hz, 1H), 3.90 (dd, $J = 5, 3$ Hz, 1H), 3.72 (dd, $J = 8, 4$ Hz, 1H), 3.68 (dd, $J = 8, 4$ Hz, 1H).

Data for **481**: ^1H NMR (300 MHz, CDCl_3): δ 7.27 (s, 1H), 7.20 (s, 1H), 4.83 (dddd, $J = 12, 8, 3, 3$ Hz, 1H), 3.87 (dd, $J = 12, 3$ Hz, 1H), 3.67 (dd, $J = 12, 4$ Hz, 1H), 3.37-3.17 (m, 2H).

Synthesis of azide **469**

To a solution of alcohol **468** (700 mg, 3.57 mmol) in CH_2Cl_2 (20 mL) at 0°C was added Et_3N , followed by the addition of MsCl (416 μL , 5.35 mmol). The mixture was stirred at 0°C for 30 min, then EtOAc (100 mL) was added, and the mixture was washed with brine (100 mL x 2), dried with MgSO_4 , and evaporated to afford the crude mesylate (800 mg).

A mixture of the above mesylate (800 mg, 3.57 mmol) and NaN_3 in DMF (15 mL) was stirred at 80°C for 3 h, then the mixture was poured into water (50 mL), extracted with Et_2O (30 mL x 3), dried with Na_2SO_4 , and evaporated to afford azide **469** (540 mg, 68% yield). Data for **469**: ^1H NMR (300 MHz, CDCl_3): δ 8.39 (s, 1H), 8.30-8.20 (m, 1H), 7.03 (dd, $J = 8, 3$ Hz, 1H), 4.40-4.30 (m, 1H), 3.60 (dd, $J = 10, 5$ Hz, 1H), 3.55-3.35 (m, 2H), 3.25 (dd, $J = 16, 7$ Hz, 1H).

Synthesis of azides **482-487**

These azides were synthesized from the appropriate alcohols using the above procedure for the synthesis of **469**.

Data for **482**: ^1H NMR (300 MHz, CDCl_3): δ 8.46 (d, $J = 3$ Hz, 1H), 7.88 (dd, $J = 9$, 2 Hz, 1H), 7.49 (dd, $J = 9$, 2 Hz, 1H), 5.00-4.80 (m, 1H), 3.53 (dd, $J = 10$, 4 Hz, 1H), 3.53-3.30 (m, 2H), 3.16 (dd, $J = 17$, 7 Hz, 1H).

Data for **483**: ^1H NMR (300 MHz, CDCl_3): δ 7.79 (d, $J = 8$ Hz, 2H), 7.68 (d, $J = 8$ Hz, 2H), 5.13-5.02 (m, 1H), 4.43 (dd, $J = 11$, 4 Hz, 1H), 4.37 (dd, $J = 11$, 5 Hz, 1H), 3.53 (dd, $J = 17$, 11 Hz, 1H), 3.33 (dd, $J = 9$, 7 Hz, 1H).

Data for **484**: ^1H NMR (300 MHz, CDCl_3): δ 7.87 (dd, $J = 9$, 9 Hz, 1H), 7.70 (d, $J = 8$ Hz, 1H), 7.56 (dd, $J = 8$, 8 Hz, 1H), 5.13-5.02 (m, 1H), 4.46-4.30 (m, 2H), 3.53 (dd, $J = 17$, 11 Hz, 1H), 3.36 (dd, $J = 9$, 7 Hz, 1H).

Data for **485**: ^1H NMR (300 MHz, CDCl_3): δ 7.65 (d, $J = 9$ Hz, 2H), 7.19 (d, $J = 8$ Hz, 2H), 4.93-4.85 (m, 1H), 3.50 (dd, $J = 13$, 5 Hz, 1H), 3.43-3.30 (m, 2H), 3.15 (dd, $J = 13$, 7 Hz, 1H).

Data for **486**: ^1H NMR (300 MHz, CDCl_3): δ 7.67-7.50 (m, 4H), 4.94-4.84 (m, 1H), 3.50 (dd, $J = 13$, 5 Hz, 1H), 3.45-3.25 (m, 2H), 3.20 (dd, $J = 13$, 7 Hz, 1H).

Data for **487**: ^1H NMR (300 MHz, CDCl_3): δ 7.67-7.50 (m, 4H), 4.94-4.84 (m, 1H), 3.50 (dd, $J = 13$, 5 Hz, 1H), 3.45-3.25 (m, 2H), 3.20 (dd, $J = 13$, 7 Hz, 1H).

Synthesis of alcohol **488**

A mixture of alcohol **348** (310 mg, 1.21 mmol), 3-(tributyl)stannylpyridine (446 mg, 1.21 mmol), $\text{Pd}(\text{dppf})_2\text{Cl}_2$ (59 mg, 0.072 mmol), copper (I) chloride (12 mg), lithium chloride (305 mg, 7.20 mmol) in DMSO (3.0 mL) was degassed by argon and then was stirred at 60°C for 16 h. The reaction was quenched by the addition of H_2O (50 mL), NH_4OH (0.2 mL), EtOAc (150 mL) and CH_2Cl_2 (20 mL). The mixture was passed through celite. The organic layer was washed with water (50 mL x 3), dried with Na_2SO_4 , and the residue was purified by flash-chromatography (eluant: $\text{MeOH}/\text{CH}_2\text{Cl}_2$, 2/100), to give **488** (265 mg). Data for **488**: ^1H NMR (300 MHz, CDCl_3): δ 8.88 (s, 1H), 8.63 (d, $J = 4$ Hz, 1H), 7.92 (d, $J = 8$ Hz, 1H), 7.89 (d, $J = 8$ Hz, 2H), 7.64 (d, $J = 8$ Hz, 1H), 7.41 (dd, $J = 8$, 5 Hz, 1H), 4.92 (dddd, $J = 12$, 8, 3, 3 Hz, 1H), 3.92 (dd, $J = 12$, 3 Hz, 1H), 3.72 (dd, $J = 12$, 5 Hz, 1H), 3.44 (dd, $J = 17$, 11 Hz, 1H), 3.33 (dd, $J = 17$, 8 Hz, 1H).

Synthesis of azide 489

The azide was synthesized using the same procedure as described above for the synthesis of azide 469. Data for 489: ¹HNMR (300 MHz, CDCl₃): δ 8.85 (s, 1H), 8.60 (m, 1H), 7.85 (d, *J* = 8 Hz, 1H), 7.73 (d, *J* = 9 Hz, 2H), 7.58 (d, *J* = 9 Hz, 2H), 7.36 (s, 1H), 4.96-4.84 (m, 1H), 3.54 (dd, *J* = 13, 5 Hz, 1H), 3.45-3.35 (m, 2H), 3.20 (dd, *J* = 13, 7 Hz, 1H).

Synthesis of alcohol 490

This compound was synthesized from alcohol 476 using the procedure described above for the synthesis of 488. Data for 490: ¹HNMR (300 MHz, CDCl₃): δ 9.17 (s, 1H), 8.86 (d, *J* = 2 Hz, 1H), 8.62 (s, 1H), 8.30 (d, *J* = 8 Hz, 1H), 8.08 (dd, *J* = 8, 2 Hz, 1H), 7.76 (d, *J* = 8 Hz, 1H), 7.37 (dd, *J* = 8, 5 Hz, 1H), 4.93-4.84 (m, 1H), 3.88 (d, *J* = 10 Hz, 1H), 3.66 (d, *J* = 10 Hz, 1H), 3.44-3.20 (m, 2H).

Synthesis of azide 491

This azide was synthesized from alcohol 490 using the same procedure described above for the synthesis of azide 469. Data for 491: ¹HNMR (300 MHz, CDCl₃): δ 8.82 (s, 1H), 8.30-8.20 (m, 2H), 8.28-8.18 (m, 2H), 7.76 (d, *J* = 9 Hz, 1H), 7.40 (s, 1H), 4.96-4.86 (m, 1H), 3.59-3.20 (m, 4H), 3.20 (dd, *J* = 13, 7 Hz, 1H).

Synthesis of silylether 493

To a solution of alcohol 460 (360 mg, 2.00 mmol) in DMF (8.0 mL) at 0°C was added *t*-butyldimethylsilyl chloride (461 mg, 3.00 mmol), followed by the addition of imidazole (275 mg, 4.0 mmol). The mixture was stirred at 0°C for 1 h and room temperature for 16 h. Water (50 mL) was added, and the mixture was extracted with 30% EtOAc in hexane (50 mL x 3). The organic phase was washed with water (50 mL x 2), dried by Na₂SO₄, and evaporated. The residue was purified by flash-chromatography (eluant: EtOAc/hexane, 5/95), to afford 493 (580 mg, 98% yield). Data for 493: ¹HNMR (300 MHz, CDCl₃, ppm): δ 4.70-4.61 (m, 1H), 3.69 (dd, *J* = 11, 4 Hz, 1H), 3.62 (dd, *J* = 11, 4 Hz, 1H), 0.81 (s, 9H), 0.01 (s, 6H).

Synthesis of azide 495

Alcohol **348** (1.00 g, 3.90 mmol) and $\text{PdCl}_2(\text{dppf})_2$ (546 mg, 0.762 mmol) were dissolved in dioxane (11 mL) and hexamethylditin (1.42 g, 4.30 mmol) was added. The mixture was stirred at 85°C for 16 h, then sat. aqueous NaHCO_3 (20 mL) was added, followed by EtOAc (20 mL). The aqueous phase was extracted with EtOAc (40 mL x 3), and the organic phase was dried by Na_2SO_4 . The residue was purified by flash-chromatography (eluant: EtOAc/hexane, 35/65) to afford stannane **492** (740 mg, 56% yield). Data for **492**: ^1H NMR (300 MHz, CDCl_3): δ 7.13 (d, J = 6 Hz, 2H), 7.05 (d, J = 6 Hz, 2H), 4.70-4.60 (m, 1H), 3.70-3.61 (m, 3H), 3.51-3.41 (m, 1H), 3.17 (dd, J = 17, 11 Hz, 1H), 3.05 (dd, J = 17, 8 Hz, 1H), 1.73 (dd, J = 8, 6 Hz, 1H), 0.09 (s, 9H).

To a suspension of stannane **492** (340 mg, 1.00 mmol), bromide **493** (353 mg, 1.20 mmol) and lithium chloride (254 mg, 6.00 mmol) in DMSO (2.5 mL) was added $\text{PdCl}_2(\text{dppf})_2$ (49 mg, 0.06 mmol). The mixture was stirred at 70°C for 16 h, then water (50 mL) was added. The mixture was extracted with EtOAc (40 mL x 3), and the extracts were dried by Na_2SO_4 . The residue was purified by flash-chromatography (eluant: EtOAc/hexane, 35/65) to afford alcohol **494** (21 mg, 63% yield). Data for **494**: ^1H NMR (300 MHz, CDCl_3): δ 7.56 (d, J = 8 Hz, 2H), 7.22 (d, J = 8 Hz, 2H), 4.90-4.81 (m, 1H), 3.87 (dd, J = 16, 3 Hz, 3H), 3.68 (dd, J = 16, 5 Hz, 1H), 3.38 (dd, J = 17, 8 Hz, 1H), 3.25 (dd, J = 17, 8 Hz, 1H), 2.38 (s, 3H).

Azide **495** was synthesized from alcohol **494** using the same procedure described above for the synthesis of azide **469**. Data for **495**: ^1H NMR (300 MHz, CDCl_3): δ 7.50 (d, J = 8 Hz, 2H), 7.15 (d, J = 8 Hz, 2H), 4.86-4.76 (m, 1H), 3.45-3.30 (m, 3H), 3.13 (dd, J = 17, 7 Hz, 1H).

General procedure for the synthesis of triazoles 394-403

To a mixture of alkyne **173** (100 mg, 0.127 mmol) and the appropriate azide (0.140 mmol, 1.1 eq) in acetonitrile (4.0 mL) at room temperature under argon was added 2,6-lutidine (22 μL , 0.191 mmol, 1.1 eq), followed by addition of copper (I) iodide (12 mg, 0.064 mmol). The mixture was stirred at room temperature for 1.5 to 6 h. After the reaction was complete, 1 mL 5% NH_4OH was added. The mixture was stirred at room temperature for 10 min. The reaction solvent (CH_3CN) was removed under vacuum. The aqueous phase was extracted with CH_2Cl_2 (30 mL x 3), and the organic phase was dried over Na_2SO_4 . The residue was separated

by flash-chromatography (eluant: 20/80 to 30/70 MeOH/EtOAc) on silica gel to afford the desired product.

Data for **394**: MS (ESI) m/z 1008.4 (M)⁺; ¹HNMR (300 MHz, CDCl₃, partial): δ 8.37 (s, 1H), 8.37-8.00 (m, 1H), 7.60 (s, 1H), 7.00 (dd, J = 9, 3 Hz, 1H), 4.45 (d, J = 6 Hz, 1H), 4.29 (br s, 1H), 2.24 (s, 3H), 1.04 (d, J = 9 Hz, 3H).

Data for **395**: MS (ESI) m/z 1070.2 (M)⁺; ¹HNMR (300 MHz, CDCl₃, partial): δ 8.45 (s, 1H), 7.73 (dd, J = 4, 2 Hz, 1H), 7.47 (d, J = 4 Hz, 1H), 4.45 (d, J = 6 Hz, 1H), 4.29 (br s, 1H), 2.20 (s, 3H), 0.98 (d, J = 9 Hz, 3H).

Data for **396**: MS (ESI) m/z 1043.7 (M)⁺; ¹HNMR (300 MHz, CDCl₃, partial): δ 7.48 (s, 1H), 7.16 (d, J = 7 Hz, 2H), 7.14 (d, J = 7 Hz, 2H), 4.36 (d, J = 7 Hz, 1H), 4.22 (s, 1H), 2.21 (s, 3H), 0.96 (d, J = 8 Hz, 3H).

Data for **397**: MS (ESI) m/z 1073.8 (M)⁺; ¹HNMR (300 MHz, CDCl₃, partial): δ 7.64 (d, J = 8 Hz, 2H), 7.24 (d, J = 8 Hz, 2H), 4.40 (d, J = 9 Hz, 1H), 4.28 (s, 1H), 2.27 (s, 3H), 1.04 (d, J = 9 Hz, 3H).

Data for **398**: MS (ESI) m/z 1073.8 (M)⁺; ¹HNMR (300 MHz, CDCl₃, partial): δ 7.53 (s, 1H), 7.43-7.34 (m, 3H), 7.22 (s, 1H), 4.36 (d, J = 7 Hz, 1H), 4.21 (s, 1H), 2.20 (s, 3H), 0.96 (d, J = 8 Hz, 3H).

Data for **399**: MS (ESI) m/z 1057.8 (M)⁺; ¹HNMR (300 MHz, CDCl₃, partial): δ 7.64 (d, J = 8 Hz, 2H), 7.58 (d, J = 8 Hz, 1H), 7.51 (br s, 1H), 4.55 (t, J = 5 Hz, 2H), 4.36 (d, J = 10 Hz, 1H), 4.21 (s, 1H), 2.25 (s, 3H), 0.95 (d, J = 8 Hz, 3H).

Data for **400**: MS (ESI) m/z 1057.8 (M)⁺; ¹HNMR (300 MHz, CDCl₃, partial): δ 7.78 (s, 1H), 7.70 (d, J = 8 Hz, 1H), 7.60 (d, J = 8 Hz, 1H), 7.53-7.44 (m, 2H), 4.46 (d, J = 7 Hz, 1H), 4.21 (s, 1H), 2.20 (s, 3H), 0.96 (d, J = 8 Hz, 3H).

Data for **401**: MS (ESI) m/z 1003.8 (M)⁺; ¹HNMR (300 MHz, CDCl₃, partial): δ 7.60 (s, 1H), 7.48 (d, J = 8 Hz, 2H), 7.19 (d, J = 8 Hz, 2H), 4.43 (d, J = 7 Hz, 1H), 4.22 (s, 1H), 2.27 (s, 3H), 1.04 (d, J = 8 Hz, 3H).

Data for **402**: MS (ESI) m/z 1066.9 (M)⁺; ¹HNMR (300 MHz, CDCl₃, partial): δ 8.79 (s, 1H), 8.56 (d, J = 4 Hz, 1H), 7.82 (dt, J = 8, 2 Hz, 1H), 7.65 (d, J = 8 Hz, 2H), 7.56 (d, J = 8 Hz, 2H), 7.53 (s, 1H), 7.33 (dd, J = 8, 4 Hz, 1H), 4.37 (d, J = 7 Hz, 1H), 4.21 (s, 1H), 2.20 (s, 3H), 0.97 (d, J = 8 Hz, 3H).

Data for **403**: MS (ESI) m/z 1067.8 (M)⁺; ¹H NMR (300 MHz, CDCl₃, partial): δ 9.16 (s, 1H), 8.62 (d, J = 4 Hz, 1H), 7.82 (dt, J = 8, 2 Hz, 1H), 7.96 (dd, J = 6, 2 Hz, 1H), 7.74 (d, J = 8 Hz, 1H), 7.51 (s, 1H), 7.37 (dd, J = 8, 5 Hz, 1H), 4.36 (d, J = 7 Hz, 1H), 4.21 (s, 1H), 2.20 (s, 3H), 0.96 (d, J = 8 Hz, 3H).

5

Example 55 – Synthesis of Triazoles 404 and 405

Synthesis of azide 404

This compound (189 mg) was synthesized from alkyne **174** (150 mg, 0.187 mmol) and azide **349** (58 mg, 0.206 mmol) using the same procedure described above for the synthesis of triazole **361**. Data for **404**: MS (ESI) m/z 542 ($M+2H$)²⁺; ¹H NMR (300 MHz, CDCl₃, partial): δ 7.53-7.50 (m, 3H), 7.45-7.42 (m, 2H), 5.17-5.11 (m, 1H), 5.08 (d, J = 4 Hz, 1H), 4.69-4.66 (m, 1H), 4.61 (t, J = 5 Hz, 2H), 4.45 (d, J = 7 Hz, 1H), 3.33 (s, 3H), 3.03 (t, J = 9 Hz, 1H), 2.21 (t, J = 5 Hz, 4H), 0.89 (m, 6H).

15 Synthesis of azide 405

This compound (175 mg) was made from alkyne **174** (150 mg, 0.187 mmol) and azide **503** (49 mg, 0.206 mmol; see Example 58 for the synthesis of **503**) using the same procedure described above for the synthesis of triazole **361**. Data for **405**: MS (ESI) m/z 520.5 ($M+2H$)²⁺; ¹H NMR (300 MHz, CDCl₃, partial): δ 7.49 (s, 1H), 7.12-7.05 (m, 2H), 6.91-6.82 (m, 1H), 5.21-5.13 (m, 1H), 5.12 (d, J = 5 Hz, 1H), 4.61 (t, J = 4 Hz, 2H), 4.44 (d, J = 7 Hz, 1H), 4.29 (br d, J = 3 Hz, 1H), 4.13-4.03 (m, 1H), 3.69 (d, J = 6 Hz, 1H), 3.65 (d, J = 7 Hz, 1H), 3.03 (t, J = 10 Hz, 1H), 0.91-0.87 (m, 6H).

20

Example 56 – Synthesis of Triazoles 406-409

These triazoles were synthesized using the procedure described above for the synthesis of triazole **228**.

25

Synthesis of triazole 406

Alkyne **174** (70 mg, 86 μ mol), azide **355** (39 mg, 129 μ mol), and CuI (2 mg, 8 μ mol) afforded triazole **406** as a white solid (94.1 mg, 83 μ mol). Data for **406**: MS (ESI) m/z 568 ($M+2H$)²⁺; ¹H NMR (300 MHz, CDCl₃, partial): δ 9.46 (br s, 1H), 7.69-7.53 (m, 8H), 7.44 (s, 1H),

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5.20-5.04 (m, 3H), 4.70-4.58 (m, 2H), 4.41 (d, $J = 6$ Hz, 1H), 4.20 (br s, 1H), 4.12-4.00 (m, 1H), 3.61 (d, $J = 3$ Hz, 1H), 3.56 (d, $J = 7$ Hz, 1H), 3.33 (s, 3H), 3.05-2.93 (m, 2H), 2.29 (s, 3H), 2.18 (s, 3H), 2.10 (d, $J = 9$ Hz, 1H), 1.34-1.14 (m, 17H), 0.91-0.84 (m, 6H): ^{13}C NMR (75 MHz, CDCl_3): δ 178.9, 156.3, 148.4, 144.4, 141.0, 132.7, 128.9, 127.6, 127.5, 127.4, 122.3, 118.6, 111.6, 102.9, 94.5, 83.3, 79.2, 78.2, 77.7, 74.2, 73.7, 73.0, 70.6, 70.1, 68.8, 65.9, 65.5, 62.4, 53.1, 52.4, 49.5, 45.3, 42.3, 37.4, 36.8, 36.2, 34.7, 29.6, 27.8, 27.6, 26.9, 26.8, 25.4, 22.0, 21.6, 21.3, 21.2, 18.2, 16.2, 14.5, 11.2, 8.8, 7.9.

Synthesis of triazole 407

Alkyne **174** (70 mg, 86 μmol), azide **349** (36 mg, 129 μmol), and CuI (2 mg, 8 μmol) afforded triazole **407** as a white solid (89 mg, 80 μmol). Data for **407**: MS (ESI) m/z 556, 557 ($M + 2\text{H}$) $^{2+}$; ^1H NMR (300 MHz, CDCl_3 , partial): δ 9.38 (br s, 1H), 7.54-7.41 (m, 5H), 7.44 (s, 1H), 5.20-4.90 (m, 3H), 4.70-4.58 (m, 3H), 4.49 (d, $J = 6$ Hz, 1H), 4.28 (br s, 1H), 4.12-4.00 (m, 1H), 3.61 (d, $J = 3$ Hz, 1H), 3.32 (s, 3H), 3.05-2.93 (m, 2H), 2.30 (s, 3H), 2.17 (s, 3H), 2.15 (d, $J = 9$ Hz, 1H), 1.33-1.27 (m, 6H), 1.27-1.15 (m, 10H), 1.10-1.00 (m, 8H), 0.91-0.84 (m, 6H): ^{13}C NMR (75 MHz, CDCl_3): δ 178.8, 156.0, 148.4, 132.0, 128.1, 127.6, 124.8, 122.3, 102.9, 94.5, 83.3, 79.2, 78.2, 77.7, 74.3, 73.7, 73.0, 70.6, 70.1, 68.8, 65.9, 65.5, 62.4, 53.4, 53.1, 52.4, 49.5, 45.3, 42.2, 37.2, 36.8, 36.2, 34.7, 29.6, 27.8, 27.6, 26.9, 26.8, 25.4, 22.0, 21.6, 21.4, 21.3, 18.2, 16.2, 14.6, 11.2, 8.9, 7.4.

Synthesis of triazole 408

Alkyne **174** (70 mg, 86 μmol), azide **158** (39 mg, 129 μmol), and CuI (2 mg, 8 μmol) afforded triazole **408** as a white solid (93 mg, 85 μmol). Data for **408**: MS (ESI) m/z 560 ($M + 2\text{H}$) $^{2+}$; ^1H NMR (300 MHz, CDCl_3 , partial): δ 7.70 (br s, 1H), 7.50 (s, 1H), 7.31 (dd, $J = 14, 2$ Hz, 1H), 7.21 (dd, $J = 8, 2$ Hz, 1H), 6.89 (t, $J = 9$ Hz, 3H), 5.14-5.05 (m, 1H), 4.97 (d, $J = 4$ Hz, 1H), 4.65-4.45 (m, 3H), 4.45 (d, $J = 7$ Hz, 1H), 4.28 (dd, $J = 6, 2$ Hz, 1H), 4.13-3.97 (m, 1H), 3.87-3.80 (m, 4H), 3.68-3.61 (m, 3H), 3.32 (s, 3H), 2.28 (s, 3H), 2.18 (d, $J = 9$ Hz, 1H), 2.13 (s, 3H), 1.35-1.15 (m, 18H), 1.10-1.02 (m, 9H), 0.91-0.82 (m, 6H): ^{13}C NMR (75 MHz, CDCl_3): δ 178.3, 153.3, 148.3, 133.4, 122.5, 122.3, 118.2, 114.5, 114.2, 103.0, 95.4, 84.0, 79.0, 78.1, 77.6, 77.5, 77.1, 76.6, 73.5, 72.8, 70.7, 70.0, 68.7, 66.7, 65.6, 65.5, 61.8, 53.1, 52.4, 50.4, 50.3, 49.4,

44.9, 42.5, 40.9, 37.4, 36.8, 36.6, 35.0, 29.7, 27.8, 27.3, 26.9, 26.7, 25.4, 21.9, 21.6, 21.4, 18.4, 16.3, 15.5, 11.2, 8.9, 7.4.

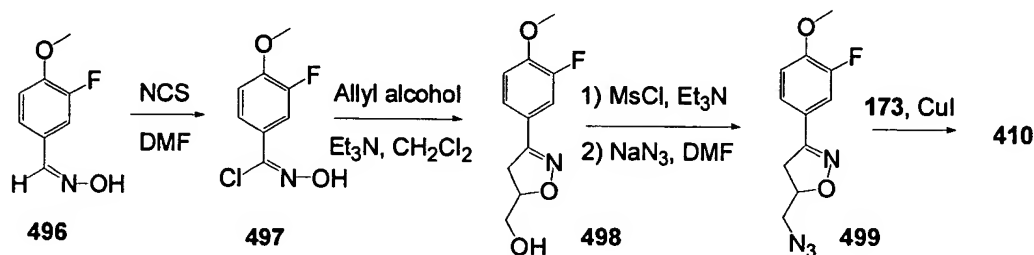
Synthesis of triazole 409

5 Alkyne **174** (70 mg, 86 μ mol), the azide **503** (31 mg, 129 μ mol; see Example 58 for the synthesis of **503**), and CuI (2 mg, 8 μ mol) afforded triazole **409** as a white solid (93 mg, 85 μ mol). Data for **409**: MS (ESI) m/z 527 ($M + 2H$)²⁺; ¹HNMR (300 MHz, CDCl₃, partial): δ 8.95 (br s, 1H), 7.47 (s, 1H), 7.12-7.03 (m, 2H), 6.71 (tt, $J = 9, 2$ Hz, 1H), 5.21-5.09 (m, 2H), 4.62 (d, $J = 6$ Hz, 1H), 4.48 (t, $J = 10$ Hz, 1H), 4.45 (d, $J = 7$ Hz, 1H), 4.29 (br s, 1H), 4.15-4.00 (m, 1H),
10 3.66 (d, $J = 5$ Hz, 1H), 3.62 (d, $J = 7$ Hz, 1H), 3.32 (s, 3H), 3.02 (t, $J = 11$ Hz, 1H), 2.29 (s, 3H), 2.18 (d, $J = 10$ Hz, 1H), 2.13 (s, 3H), 1.77 (d, $J = 9$ Hz, 1H), 1.33-1.26 (m, 6H), 1.27-1.15 (m, 10H), 1.10-0.99 (m, 9H), 0.92-0.84 (m, 6H): ¹³CNMR (75 MHz, CDCl₃, partial): δ 178.7, 155.2, 148.4, 131.6, 122.2, 109.9, 109.8, 109.6, 109.5, 105.7, 102.9, 94.6, 83.4, 79.6, 78.1, 77.9, 76.6, 74.3, 73.9, 73.6, 72.9, 70.6, 70.1, 68.8, 65.8, 65.5, 62.3, 53.1, 52.3, 49.4, 45.2, 42.4, 42.0, 37.0,
15 36.8, 36.3, 34.8, 29.6, 27.8, 27.5, 27.0, 26.7, 25.4, 21.9, 21.6, 21.3, 21.2, 18.2, 16.2, 11.2, 7.5.

Example 57 – Synthesis of Triazoles 410 and 411

These triazoles were synthesized using the chemistry illustrated for triazole **410** shown in Scheme 77. Racemic azide **499** was used to generate triazole **410** as a mixture of diastereomers.

Scheme 77



Synthesis of azide 499

25 A solution of 3-fluoro-4-methoxybenzaldehyde (2.0 g, 12.97 mmol) and hydroxylamine hydrochloride (1.0 g, 14.27 mmol) in ethanol (40 mL) and water (80 mL) was cooled to 4 °C, and 2.3 mL NaOH (50% w/w) was added. The reaction mixture was stirred for 3 h at room

temperature. The reaction mixture was adjusted to pH 6.0, and partitioned with methylene chloride and water. The aqueous layer was extracted twice with methylene chloride, and the combined organic layer was washed with brine, dried (Na₂SO₄), and evaporated to yield **496** (1.97 g, 90%) as a white solid. Data for **496**: ¹HNMR (300 MHz, CDCl₃): δ 7.84 (s, 1H), 7.04 (d, *J* = 3 Hz, 1H), 6.74 (app t, *J* = 8 Hz, 1H).

To a solution of oxime **496** (1.97 g, 11.64 mmol) in dimethylformamide (10 mL) was added *N*-chlorosuccinimide (1.5 g, 11.64 mmol). The reaction mixture was warmed to 50°C for 1 h. The reaction was diluted with ethyl acetate (50 mL), and washed with brine. The organic phase was dried (Na₂SO₄), and evaporated to yield **497** (2.37 g, 100% yield). Data for **497**: ¹HNMR (300 MHz, CDCl₃): δ 8.02 (s, 1H), 7.60 (m, 1H), 6.94 (t, *J* = 3 Hz, 1H).

To a solution of hydroximinoyl chloride **497** (1.00 g, 4.91 mmol) in methylene chloride (5 mL) was added allyl alcohol (0.3 mL, 4.91 mmol). The mixture was cooled to 0°C, and triethylamine (0.68 mL, 4.91 mmol) was added. The reaction mixture was slowly warmed to room temperature, stirred for 16 h, then quenched with water (20 mL), and extracted twice with methylene chloride. The combined organic layer was washed with brine, dried over (Na₂SO₄), and evaporated to yield **498** (0.76 g, 70% yield). Data for **498**: ¹HNMR (300 MHz, CDCl₃): δ 7.40 (m, 1H), 7.30 (m, 1H), 6.80 (m, 1H), 4.80 (m, 1H), 3.60 (s, 3H), 3.20 (m, 2H).

Alcohol **498** (0.7 g, 3.10 mmol) was dissolved in 10 mL methylene chloride, and the mixture cooled to 0°C. Triethylamine (0.86 mL, 6.2 mmol) was added, followed by methanesulfonyl chloride (0.34 mL, 4.35 mmol). The mixture was allowed to warm to room temperature and stirred for 1 h. Methylene chloride (10 mL) was added, and the mixture washed twice with 1N HCl, then twice with 10% aqueous sodium carbonate, and then brine. The organic phase was dried (Na₂SO₄), and evaporated to yield the expected mesylate (0.77 g, 86% yield). Data: ¹HNMR (300 MHz, CDCl₃): δ 7.40 (m, 1H), 7.20 (d, *J* = 3 Hz, 1H), 6.85 (m, 1H), 4.90 (m, 1H), 3.00 (s, 3H).

A solution of the above mesylate (0.77 g, 2.30 mmol) in dimethylformamide (5 mL) was treated with sodium azide (0.66 g, 10.15 mmol) and the mixture heated to 80°C for 3 h. The reaction mixture was cooled to room temperature, diluted with ethyl acetate (50 mL), and washed with brine (2 x 50 mL). Drying (Na₂SO₄), and evaporation provided azide **499** (0.52, 83% yield) as a yellow oil of suitable purity for use in subsequent reactions.

Synthesis of triazole 410

A solution of alkyne **173** (100 mg, 0.127 mmol) in tetrahydrofuran (10 mL) was treated with azide **499** (0.05 g, 0.19 mmol), *N,N*-diisopropylethylamine (0.03 mL, 0.15 mmol) and copper (I) iodide (0.02 g, 0.127 mmol), and the mixture was stirred under argon at room temperature for 16 h. The reaction mixture was diluted with ethyl acetate (50 mL), and washed with brine (2 x 50 mL). The organic phase was dried and evaporated. The residue was purified by preparative thin layer chromatography (using 90% CH₂Cl₂, 0% MeOH, 0.1 % NH₄OH as eluant) to provide **410** (71 mg, 77% yield) as a yellow solid. Data for **410**: ¹H-NMR (300 MHz, CDCl₃, partial): δ 7.50 (s, 1H), 7.32 (m, 1H), 7.10 (s, 1H), 6.80 (t, *J* = 3 Hz, 1H), 5.0 (m, 1H), 4.60-4.35 (m, 2H), 4.01 (m, 1H), 3.6 (m, 1H).

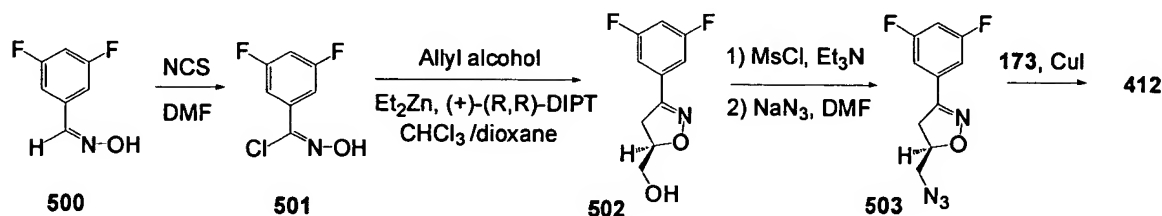
Synthesis of triazole 411

This compound was made from alkyne **173** and the required 3-(4-chlorophenoxy)phenyl isoxazoline azide (synthesized from 3-(4-chlorophenoxy)benzaldehyde using the same procedure described above for the synthesis of azide **499**) using the same procedure described above for the synthesis of triazole **410**. Data for **411**: ¹H-NMR (300 MHz, CDCl₃, partial): δ 7.50 (s, 1H), 7.10-7.30 (m, 4H), 6.90 (s, 1H), 6.80 (s, 1H), 5.02 (m, 1H), 4.50-4.70 (m, 2H), 4.35 (d, *J* = 3 Hz, 1H), 4.0 (m, 1H), 3.60 (t, *J* = 7 Hz, 2H).

Example 58 – Synthesis of Triazoles 412-414

These triazoles were synthesized using the chemistry illustrated for triazole **412** shown in Scheme 78. Hydroxyiminoyl chloride **501** was converted to chiral, non-racemic alcohol **502** which was transformed to azide **503**. The cycloaddition of alkyne **173** with azide **503** yielded triazole **412**.

Scheme 78



Synthesis of azide 503

A solution of 3,5-difluorobenzaldehyde (2.0 g, 14.0 mmol) and hydroxylamine hydrochloride (1.07 g, 15.4 mmol) in ethanol (40 mL) and water (80 mL) was cooled to 4°C, and 2.3 mL NaOH (50% w/w) was added. The reaction mixture was stirred for 3 h at room temperature. The reaction mixture was adjusted to pH 6.0, and partitioned with methylene chloride and water. The aqueous layer was extracted twice with methylene chloride, and the combined organic layer was washed with brine, dried (Na₂SO₄), and evaporated to yield **500** (2.01 g, 91% yield) as a white solid. Data for **500**: ¹HNMR (300 MHz, CDCl₃): δ 7.82 (s, 1H), 6.80 (m, 1H), 6.60 (m, 1H).

To a solution of oxime **500** (2.01 g, 12.7 mmol) in dimethylformamide (10 mL) was added *N*-chlorosuccinimide (1.7 g, 12.7 mmol). The reaction mixture was warmed to 50°C for 1 h. The reaction was diluted with ethyl acetate (50 mL), and washed with brine. The organic phase was dried (Na₂SO₄), and evaporated to yield **501** (2.45 g, 100% yield). Data for **501**: ¹HNMR (300 MHz, CDCl₃): δ 8.0 (s, 1H), 7.40 (d, *J* = 2 Hz, 1H), 6.80 (m, 1H).

To a solution of allyl alcohol (0.7 mL, 10.30 mmol) in 20 mL CHCl₃ was added a 1 M diethylzinc solution in hexane (12.4 mL, 12.40 mmol) at -5 to 0°C. After stirring for 10 min, (+)-diisopropyl tartrate (0.5 mL, 2.10 mmol) was added and the solution was stirred for 1 h at 0°C. The milky solution was cooled to -20°C and 20 mL CHCl₃ and dioxane (5 mL) was added. Then hydroximinoyl chloride **501** (1.80 g, 9.40 mmol) was added in portions at -20 to -15°C. The solution was stirred for 3 h at -150°C, then poured into 100 mL saturated aqueous NH₄Cl and extracted with CHCl₃ (3 X 100 mL). The combined organic extract was washed with brine, dried Na₂SO₄, and evaporated. The residue was purified by flash-chromatography (eluting with 30 % ethyl acetate/hexane), to afford crude material which was recrystallized from ethyl acetate and hexane to yield **502** (0.75 g, 75% yield). Data for **502**: ¹HNMR (300 MHz, CDCl₃): δ 7.20 (m, 2H), 6.80 (m, 1H), 4.96 (m, 1H), 3.90 (m, 1H), 3.70 (m, 1H), 3.30 (m, 2H), 2.10 (m, 1H).

Alcohol **502** (0.74 g, 3.47 mmol) was dissolved in 10 mL methylene chloride, and the mixture cooled to 0°C. Triethylamine (1.0 mL, 6.94 mmol) was added, followed by methanesulfonyl chloride (0.4 mL, 4.85 mmol). The mixture was allowed to warm to room temperature and stirred for 1 h. Methylene chloride (10 mL) was added, and the mixture washed twice with 1 N HCl, then twice with 10% aqueous sodium carbonate, and then brine. The organic phase was dried (Na₂SO₄), and evaporated to yield the mesylate (0.93 g, 92% yield).

Data: ¹HNMR (300 MHz, CDCl₃): δ 7.15 (m, 2H), 6.85 (m, 1H), 5.01 (m, 1H), 4.33 (m, 2H), 3.00 (s, 3H)

A solution of the above mesylate (0.93 g, 3.19 mmol) in dimethylformamide (10 mL) was treated with sodium azide (0.83 g, 12.7 mmol) and the mixture heated to 80°C for 3 h. The reaction mixture was cooled to room temperature, diluted with ethyl acetate (50 mL), and washed with brine (2 x 50 mL). Drying (Na₂SO₄), and evaporation provided azide **503** (0.65, 86% yield) as a yellow oil of suitable purity for use in subsequent reactions. Data for **503**: ¹HNMR (300 MHz, CDCl₃): δ 7.20 (m, 2H), 6.80 (m, 1H), 4.95 (m, 1H), 3.54 (dd, *J* = 4, 15 Hz, 1H), 3.00 (dd, *J* = 7, 10 Hz, 1H).

Synthesis of triazole **412**

A solution of alkyne **173** (100 mg, 0.127 mmol) in tetrahydrofuran (10 mL) was treated with azide **503** (0.045 g, 0.19 mmol), *N,N*-diisopropylethylamine (0.03 mL, 0.15 mmol) and copper (I) iodide (0.02 g, 0.127 mmol), and the mixture was stirred under argon at room temperature for 16 h. The reaction mixture was diluted with ethyl acetate (50 mL), and washed with brine (2 x 50 mL). The organic phase was dried and evaporated. The residue was purified by preparative thin layer chromatography (using 80% CH₂Cl₂, 20% MeOH, 0.1 % NH₄OH as eluant) to provide **412** (96 mg, 74% yield) as a yellow solid. Data for **412**: ¹HNMR (300 MHz, CDCl₃, partial): δ 8.50 (s, 1H), 7.10 (m, 1H), 7.00 (m, 1H), 6.80 (m, 1H), 5.10 (m, 1H), 4.70-4.50 (m, 2H), 4.01 (m, 1H), 3.80 (m, 1H).

Synthesis of triazole **413**

This compound was made from alkyne **173** and the required 3,5-dichlorophenyl isoxazoline azide (produced from 3,5-dichlorobenzaldehyde as described above for the synthesis of azide **503**) using the same procedure described above for the synthesis of **412**. Data for **413**: ¹H-NMR (300 MHz, CDCl₃, partial): δ 9.20 (s, 1H), 7.50 (m, 1H), 7.35 (m, 1H), 5.10 (m, 2H), 4.90 (m, 1H), 4.60 (d, *J* = 5 Hz, 1H), 4.50 (m, 2H), 4.40 (d, *J* = 3 Hz, 1H), 4.00 (m, 1H), 3.60 (m, 2H), 3.20 (s, 3H).

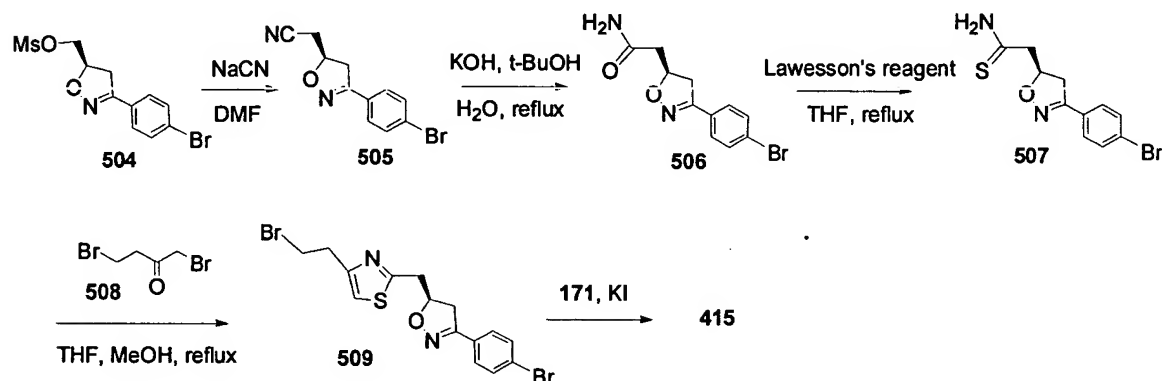
Synthesis of triazole **414**

This compound was made from alkyne **173** and the required piperonyl isoxazoline azide (produced from piperonaldehyde as described above for the synthesis of azide **503**) using the same procedure described above for the synthesis of **412**. Data for **414**: ¹H-NMR (300 MHz, CDCl₃, partial): δ 8.80 (s, 1H), 7.30 (m, 1H), 7.20 (s, 1H), 7.00 (m, 1H), 6.80 (m, 1H), 6.0 (s, 1H), 4.95 (m, 2H), 4.80-4.20 (m, 8H), 4.00 (m, 1H), 3.70 (t, *J* = 3 Hz, 3H).

Example 59 – Synthesis of Thiazole **415**

Scheme 79 depicts the synthesis of thiazole **415**. Mesylate **504** was converted to nitrile **505** which was then hydrolyzed to afford amide **506**. Amide **506** was treated with Lawesson's reagent to give the thioamide **507**, which was subsequently converted to thiazole **509** by heating in the presence of acyl bromide **508**. Alkylation of amine **171** then provided thiazole **415**.

Scheme 79



Synthesis of bromide **509**

Under an argon atmosphere, a mixture of mesylate **504** (1.67 g, 5 mmol; for a synthesis see Example 39) and NaCN (1.25 g, 25 mmol) in 15 mL of DMF was heated at 120°C for 2 h. The reaction mixture was diluted with EtOAc, washed with brine, dried (MgSO₄), concentrated and crystallized in EtOAc/hexane to afford nitrile **505** (1.20 g, 90% yield). Data for **505**: ¹H-NMR (300 MHz, CDCl₃): δ 7.56 (d, *J* = 9 Hz, 2H), 7.53 (d, *J* = 9 Hz, 2H), 5.05 (m, 1H), 3.60 (dd, *J* = 11, 17 Hz, 1H), 3.25 (dd, *J* = 6, 17 Hz, 1H), 2.51 (dd, *J* = 5, 17 Hz, 1H), 2.73 (dd, *J* = 7, 17 Hz, 1H).

A mixture of nitrile **505** (1.0 g, 3.77 mmol) and KOH (0.5 g, 8.93 mmol) in 16 mL of tert-butanol and 2 mL of water was heated to reflux for 2 h. The reaction mixture was cooled to

room temperature and diluted with water. The desired amide **506** was collected by filtration (0.85 g, 80% yield). Data for **506**: ^1H NMR (300 MHz, DMSO): δ 7.66 (d, J = 8 Hz, 2H), 7.61 (d, J = 8 Hz, 2H), 7.43 (s, 1H), 6.97 (s, 1H), 4.99 (m, 1H), 3.52 (dd, J = 11, 17 Hz, 1H), 3.15 (dd, J = 7, 17 Hz, 1H), 2.51 (dd, J = 7, 14 Hz, 1H), 2.39 (dd, J = 7, 14 Hz, 1H).

5 A mixture of **506** (220 mg, 0.78 mmol) and Lawesson's reagent (187 mg, 0.46 mmol) in THF (3 mL) was refluxed under argon for 2 h. The reaction was diluted with EtOAc, washed with brine, dried over MgSO_4 and concentrated under vacuum. Recrystallization of the crude product from EtOAc afforded **507** (180 mg, 77 % yield). Data for **507**: MS (ESI) m/z 298.8 ($\text{M}+\text{H}$) $^+$; ^1H NMR (300 MHz, CDCl_3): δ 7.56 (d, J = 9 Hz, 2H), 7.52 (d, J = 9 Hz, 2H), 7.46 (br
10 s, 2H), 5.15 (m, 1H), 3.52 (dd, J = 10, 17 Hz, 1H), 3.27 (dd, J = 8, 17 Hz, 1H), 3.12 (d, J = 12 Hz, 2H).

To a solution of **508** (190 mg, 0.83 mmol; prepared as in *Eur. J. Org. Chem.* 2001, pp. 3789-3795) in THF (8 mL) and MeOH (2 mL) was added **507** (150 mg, 0.50 mmol). After refluxing for 2 h, the reaction was concentrated and crystallized in CH_2Cl_2 to provide **509** (163
15 mg, 77% yield). Data for **509**: MS (ESI) m/z 430.7 ($\text{M}+\text{H}$) $^+$; ^1H NMR (300 MHz, CDCl_3): δ 7.56 (d, J = 9 Hz, 2H), 7.52 (d, J = 9 Hz, 2H), 7.41 (s, 1H), 5.26 (m, 1H), 4.02 (dd, J = 4, 15 Hz, 1H), 3.85-3.75 (m, 3H), 3.69-3.47 (m, 4H).

Synthesis of thiazole **415**

20 A mixture of **509** (56 mg, 0.13 mmol), amine **171** (96 mg, 0.13 mmol), Hunig's base (170 mg, 1.3 mmol) and KI (22 mg, 0.13 mmol) in THF (4 mL) was refluxed for 24 h. The THF was removed under vacuum and the residue was dissolved in EtOAc. The solution was washed with brine, dried over MgSO_4 , concentrated and purified by chromatography on silica gel (eluant: 25:1:0.1/ CH_2Cl_2 :MeOH: $\text{NH}_3\cdot\text{H}_2\text{O}$) to provide thiazole **415** (52 mg, 37% yield). Data for **415**:
25 MS (ESI) m/z 1083.7 ($\text{M} + \text{H}$) $^+$, 542.2 (100%); ^1H NMR (300 MHz, CDCl_3 , partial): δ 7.46 (s, 4H), 6.78 (s, 1H), 5.10 (m, 1H), 3.24 (s, 3H), 0.83 (t, J = 7 Hz, 3H).

INCORPORATION BY REFERENCE

The entire disclosure of each of the patent documents and scientific articles referred to
30 herein is incorporated by reference for all purposes.

EQUIVALENTS

5 The invention may be embodied in other specific forms without departing from the spirit or essential characteristics thereof. The foregoing embodiments are therefore to be considered in all respects illustrative rather than limiting on the invention described herein. Scope of the invention is thus indicated by the appended claims rather than by the foregoing description, and all changes that come within the meaning and range of equivalency of the claims are intended to be embraced therein.